ARCHIVES of INTERNAL MEDICINE

VOLUME 76 SEPTEMBER 1945 NUMBER 3

COPYRIGHT, 1945, BY THE AMERICAN MEDICAL ASSOCIATION

ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

LOWELL A. RANTZ, M.D.; PAUL J. BOISVERT, M.D., AND WESLEY W. SPINK, M.D.

SAN FRANCISCO NEW HAVEN, CONN. MINNEAPOLIS

Rheumatic fever is the cause of much disability and of many deaths resulting from the acute process and from the chronic heart disease which so frequently follows. The investigation of preventive and therapeutic measures for the control of this serious disease has been greatly hampered by the failure of many studies to establish satisfactorily its etiology and pathogenesis.

During the past twenty years it has become increasingly apparent that infection by hemolytic streptococci is in some way related to the development of the rheumatic state. The evidence on which this fact has been based has been of an indirect nature and may be summarized as follows: 1. Rheumatic fever has been observed to follow known hemolytic streptococcus infections, particularly of the respiratory tract. In these circumstances it has been noted that the initial acute illness is usually followed by a latent or quiescent period, which terminates in the more or less explosive appearance of arthritis or carditis.[1] 2. Epidemics of rheumatic fever often follow outbreaks of scarlet fever or streptococcic sore throat.[2] 3. Recrudescences of activity frequently appear when infection by hemolytic streptococci occurs in persons who have previously undergone attacks of rheumatic fever.[3] 4. Immunologic investigations have indicated that high titers of various antistreptococcus antibodies and cutaneous hypersensitivity to products and fractions of hemolytic streptococci are usually demonstrable in persons suffering from acute rheumatic fever or from recurrences of this disease.[4]

A further approach to the problem lay in the detailed study of large groups of persons in whom hemolytic streptococcus infections of the respiratory tract had occurred, for the purpose of determining the natural history of such infections and their relationship to the rheumatic state. This approach has rarely been possible in civilian practice, because prolonged and intimate follow-up of the infected group is necessary. It became clear, with the onset of the present war and the rapid mobilization of large numbers of troops, that in certain areas hemolytic streptococcus disease of the respiratory tract and rheumatic fever

Colonel T. E. Harwood Jr., Major James Blanton and Captain Howard Coggeshall cooperated and assisted in this work.

The laboratories of the Department of Medicine, Stanford University School of Medicine, were made available to the Commission on Hemolytic Streptococcal Infections for certain studies.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1. (*a*) Escherich, T., and Schick, B.: Scharlach, Vienna, A. Hölder, 1912. (*b*) Schlesinger, B.: The Relationship of Throat Infection to Acute Rheumatism in Childhood, Arch. Dis. Childhood **5**:411, 1930.

2. Paul, J. R. and others: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, New York, Metropolitan Life Insurance Company for the American Heart Association, 1943.

3. (*a*) Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931. (*b*) Collis, W. R. F.: Acute Rheumatism and Haemolytic Streptococci, Lancet **1**:1341, 1931. Jones, T. D., and Mote, J. R.: The Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, J. A. M. A. **113**:898 (Sept. 2) 1939.

4. Todd, E. W.: Antihaemolysin Titers in Haemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, Brit. J. Exper. Path. **13**:248, 1932. Coburn, A. F., and Pauli, R. H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process: III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, J. Exper. Med. **56**:651, 1932. Boisvert, P. J.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940. Mote, J. R., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever and Rheumatoid Arthritis, J. Immunol. **41**:35, 61 and 87, 1941. Swift, H. F., and Cohn, A. E.: Type Specific Anti-M Precipitins in Rheumatic and Non-Rheumatic Patients with Hemolytic Streptococcal Infections, Proc. Soc. Exper. Biol. & Med. **34**:849, 1936. Collis, W. R. F.; Sheldon, W., and Grayhill, N.: Cutaneous Reactions in Acute Rheumatism, Quart. J. Med. **1**:511, 1932. Gibson, H. J.; Thomson, W. A. R., and Stewart, D.: The Haemolytic Streptococcus as a Factor in the Causation of Acute Rheumatism, Arch. Dis. Childhood **8**:57, 1933. Taran, L. M.; Jablon, J. M., and Weyr, H. N.: Immunologic Studies in Rheumatic Fever: I. Cutaneous Response to Type-Specific Proteins of the Hemolytic Streptococcus, J. Immunol. **49**:209, 1944. Coburn.[3a]

were prevalent. A program was therefore established in an army camp in such an area, with the assurance that a large number of infected persons would be available for study. The homogeneity of the group as to age, sex and degree of exposure to infectious agents and their availability for prolonged follow-up suggested that useful information would be obtained. In addition, various immunologic methods had been perfected for the study of antibody response [4] in infected persons and for the accurate subdivision of the hemolytic streptococci into groups and, of greatest importance, into types.[5] These technics permitted more precise study of disease caused by these organisms than had hitherto been possible.

This paper is a summary of the bacteriologic and clinical results of this work so far as it bears on the pathogenesis of rheumatic fever. Much information was obtained in regard to the bacteriology, immunology, nature and treatment of the acute initial phase of hemolytic streptococcus sore throat and of complications following this streptococcic condition, which will be presented elsewhere.

PLAN OF STUDY

All patients suffering from disease of the respiratory tract of any type were admitted to certain wards in the station hospital, where they were seen by one of us. A history was obtained, a physical examination performed, cultures of materials from the throat and nose made and a Dick test done. Patients discovered, on clinical and bacteriologic grounds, to be suffering from infection by hemolytic streptococci were transferred to special wards, where a permanent trained nursing staff was maintained, which permitted the execution of therapeutic and other investigative programs. These patients were studied by means of a variety of laboratory procedures. Cultures were made repeatedly from materials from the nose and throat, and the isolated hemolytic streptococci were classified serologically by the precipitin technics of Lancefield.[5] Serial white blood cell counts, erythrocyte sedimentation rates (Westergren) and electrocardiograms were obtained. Each patient was studied for not less than three weeks and frequently for a longer period.

RESULTS

During the period of intensive study, from Jan. 1 to April 15, 1944 approximately 1,500 patients came under observation. Group A hemolytic streptococci were not isolated from the throats of 871 patients, whose disease processes may definitely be regarded as nonstreptococcic in origin. Four hundred and ten were considered to be infected by group A streptococci, because large numbers of these organisms were recovered from the nasopharynx and because the physical examinations revealed some combination of the following signs: (1) tonsillar exudate, (2) edema and redness of the pharyngeal tissues and (3) adenitis of the anterior cervical lymph nodes, with tenderness.[5a] Three hundred persons suffered from illnesses somewhat more difficult to classify. Many of these were patients with clinically typical virus infections who were nasopharyngeal carriers of hemolytic streptococci. There were also many cases of pneumococcic pneumonia and of the ordinary communicable diseases.

Rheumatic fever never followed any of the 1,100 infections definitely or probably not of streptococcic origin. It did appear in 15 of the 410 men with infections due to group A hemolytic streptococci.

It is, therefore, clear that infection by hemolytic streptococci always preceded the development of rheumatic fever in this group. Further information as to the nature and pathogenesis of this disease was obtained by the detailed study of a large number of cases of hemolytic streptococcus sore throat and of scarlet fever. The intensive program just described was carried out in 296 cases of these diseases, serial electrocardiograms being obtained in 185. Very early in the course of this investigation it became apparent not only that typical rheumatic fever was occurring occasionally in some men of this group, but that many others were failing to return to a full state of health after the acute phase of the initial streptococcic disease. In some, the continuing activity of the disease process was caused by local suppuration, such as sinusitis and otitis media. In many, however, no evidence of such complications could be discovered. Electrocardiographic evidence of carditis was discovered in certain of these cases. It is, therefore, desirable to describe the natural history of acute streptococcic sore throat as it was observed during this study, with special reference to the period after the initial suppurative phase of the disease had subsided. Patients with and without rash are included together for the purpose of this analysis.

THE POSTSTREPTOCOCCIC STATE

Rheumatic Fever.—Rheumatic fever, characterized by migrating polyarthritis, fever, rapid erythrocyte sedimentation rate and, in 8 cases, electrocardiographic evidence compatible with the presence of carditis, developed in 15 of the

5. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941.

5a. A significant antistreptolysin and/or antifibrinolysin response occurred in 87.5 per cent of 342 of these patients, for whom suitable serial determinations were made, indicating that the clinical diagnosis was usually correct.

men previously known to have suffered from acute hemolytic streptococcus sore throat. Such a syndrome was never observed following any type of nonstreptococcic disease of the respiratory tract. Twelve of these cases were studied in detail.

It seemed possible that an analysis of these observations might suggest some of the mechanisms involved in the pathogenesis of this disorder. No serologic type of hemolytic streptococcus appeared to be more likely than others to incite the rheumatic state, and it followed initial illnesses of the respiratory tract of wide degrees of severity. Certain facts did emerge, however, which may be summarized.

Absence of Latent Period.—Previous studies have indicated that rheumatic fever does not immediately follow an acute streptococcic disease of the respiratory tract but is separated from it by a latent, or quiescent, period of one to two weeks in duration, and it has been implied that during this interval the patients are clinically well. Such was not usually the case in this group. Evidence of continuing activity of a disease process for fourteen to forty days during the so-called latent period before the appearance of fever and arthritis was obtained from 9 of the patients. In each instance the erythrocyte sedimentation rate remained above 30 mm. per hour. This course is to be contrasted with the usual course of acute hemolytic streptococcus sore throat, in which the erythrocyte sedimentation rate has returned to normal within two to three weeks. Several of these men also failed to make a complete clinical recovery, in that easy fatigability persisted after the acute illness of the respiratory tract had subsided.

Also of considerable interest was the discovery of electrocardiographic evidence of carditis several days to weeks before the development of arthritis. Abnormal electrocardiograms were obtained on the ninth, thirty-sixth and twenty-third days after the onset of the acute sore throat in 3 cases, but arthritis was not observed until five, nineteen and fifty-two days later. These facts can be emphasized by the presentation of a case record.

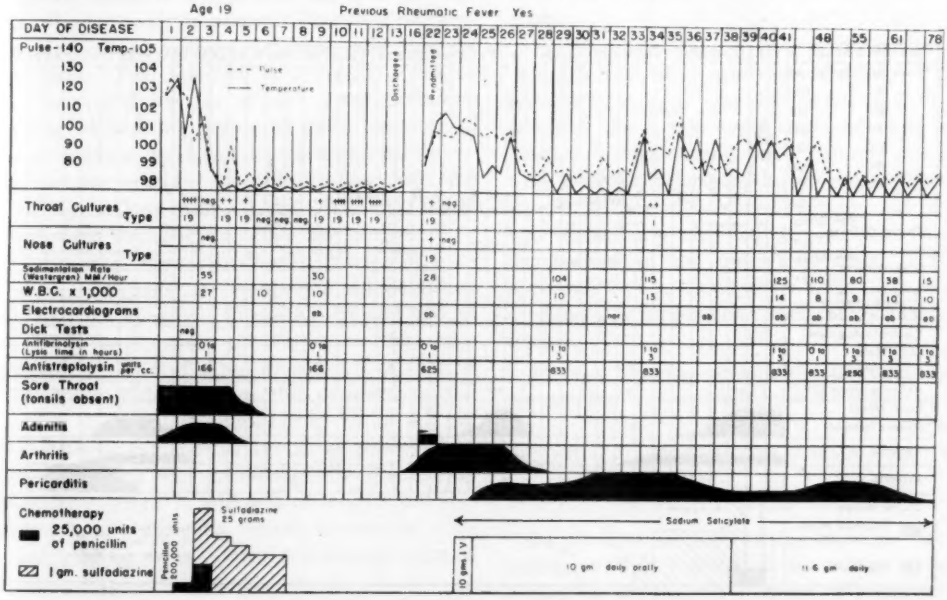

Chart 1.—The clinical course of acute hemolytic streptococcus sore throat followed by rheumatic fever, demonstrating the absence of a latent period and the early appearance of carditis.

CASE 1.—A 19 year old youth, who gave a past history of rheumatic fever at the age of 14, was admitted to the hospital on the first day of a type 19 hemolytic streptococcus sore throat. His subsequent course is presented in chart 1. The acute illness subsided rapidly after the administration of penicillin and sulfadiazine; the leukocyte count returned to normal, and the erythrocyte sedimentation rate on the ninth day had fallen to 30 mm. per hour. At this time he felt fairly well, but electrocardiographic evidence of carditis in the form of sharp inversion of the T waves in all leads was discovered. He was discharged from the hospital, and five days later the left ankle became painful. His symptoms became more severe over a period of six days, and fever appeared. At this time he reentered the hospital and was found to have an acute polyarthritis involving the knees and ankles. The temperature was 102 F., the erythrocyte sedimentation rate 28 mm. per hour and the electrocardiogram inden-

tical with that obtained on the ninth day. His disease became more active and ran the course of severe rheumatic fever with pericarditis. The latter condition was little improved by the administration of large amounts of sodium salicylate. The electrocardiogram remained abnormal for more than ninety days.

Comment.—This was a patient in whom definite evidence of activity of a disease process, in the form of a rapid erythrocyte sedimentation rate and carditis, was demonstrated to be present during the quiescent interval between the acute sore throat and the appearance of arthritis.

These observations, together with others to be presented later, indicate that certain phases of the rheumatic state are initiated soon after the initial illness of the respiratory tract and that the conception of a latent period is in part erroneous. In 3 of the 4 persons in whom a new types of hemolytic streptococci, and these cases require special comment.

Both types were present early in the initial illness of 1 patient, and the exact significance of their presence then is difficult to evaluate. In 2, both of whom exhibited a true latent period, types of hemolytic streptococci different from that causing the initial illness were present in the throat at the time of the onset of arthritis. It seemed possible that reinfection by this new strain might have incited the rheumatic process. That this could be the case is suggested by the course of events in case 2, the clinical course of which is illustrated in chart 2.

CASE 2.—A 19 year old youth entered the hospital on the first day of an acute hemolytic streptococcus sore throat, caused by an organism of type 3, from which

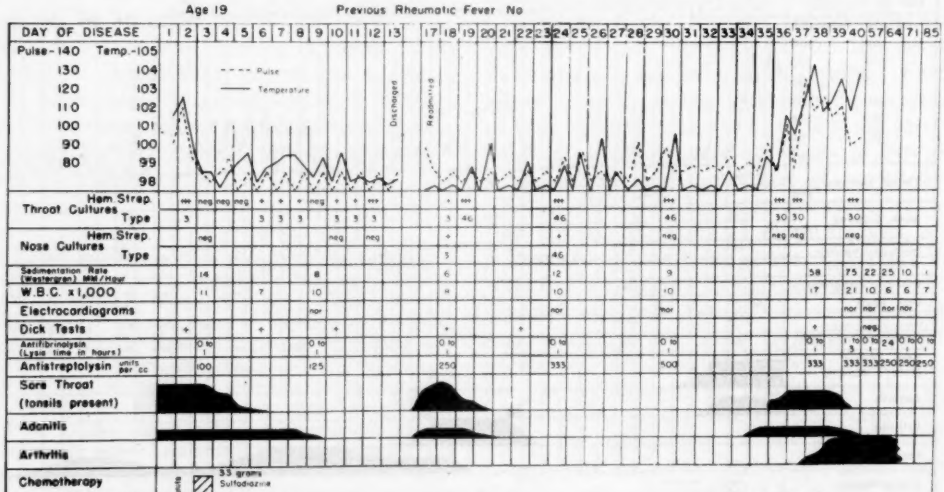

Chart 2.—The clinical course of acute hemolytic streptococcus sore throat followed by rheumatic fever after two reinfections by different serologic types.

definite latent period was observed, activation of the rheumatic disease may have been induced by a reinfection with a new type of hemolytic streptococcus (different from the one involved in the previous infection).

Reinfection by New Types of Hemolytic Streptococci.—Rheumatic fever developed in 6 persons in whom infection by only one serologic type of group A streptococcus was demonstrated. A past history of rheumatic fever was obtained for 2, and for 5 a definite latent period was absent. Case 1, just cited, is an example of this type of reaction to streptococcic infection. In 3 patients there was bacteriologic, and in 3 bacteriologic and clinical, evidence of reinfection by

he made an uneventful recovery after therapy with penicillin and sulfadiazine. Nineteen days after the onset of the initial illness he reentered the hospital, suffering from another acute sore throat due to type 46 streptococci. Recovery again occurred, and the erythrocyte sedimentation rate remained normal until two weeks later, when a sore throat due to a strain of type 30 developed. High fever and severe polyarthritis appeared thirty-six hours later, and the subsequent course was that of rheumatic fever without evidence of carditis.

Comment.—Rheumatic fever developed within thirty-six hours after the last of three acute hemolytic streptococcus sore throats, each of which had been caused by a different serologic type.

In 2 other cases, definite clinical as well as bacteriologic evidence of reinfection by new types on two or three occasions was obtained.

In 1, arthritis appeared seven days after the last acute episode. The other was different, in that the erythrocyte sedimentation rate remained above 40 mm. per hour for two weeks after two attacks of sore throat caused by types 30 and 36 and carditis was demonstrable by electrocardiography, but arthritis did not manifest itself until forty days after the subsidence of the second attack. A third strain, of type 19, was discovered in the pharynx during this interval.

These observations suggest that reinfection by hemolytic streptococci may be important in the pathogenesis of the rheumatic state. This possibility will be further discussed in another section.

Certain patients convalescent from group A streptococcic sore throat, with signs and symptoms similar to some of those observed in rheumatic fever but without arthritis, will now be described. Two hundred and twenty-seven, or 76.6 per cent of the whole group, including patients with every degree of initial severity of illness, made a rapid and complete clinical recovery, and the erythrocyte sedimentation rate was found to be less than 20 mm. per hour three weeks after the onset of acute illness.

Continuing Disease Without Arthritis or Carditis.—In 34 cases the erythrocyte sedimentation rate had not returned to normal by the end of the third week after the onset of the acute illness. No clinical signs of continuing disease were discovered in 20 of the patients, or 6.7 per cent of the total group, but in 14, or 4.7 per cent, definite evidence of an active process was obtained. This was manifested by fever, easy fatigability, anorexia and loss of weight and frequently was sufficiently severe to require continued rest in bed. Serial electrocardiograms in this group were normal.

Continuing Disease with Carditis.—In 10.8 per cent of the group of 185 cases in which serial electrocardiograms were performed, or 20 cases, a syndrome similar to that just described was observed, with the difference that definite electrocardiographic evidence of carditis was discovered. In certain cases this consisted of prolonged and changing PR intervals; in others, of sharp inversions of the T waves, usually in all three leads, and in a few of a combination of these signs. Frequently, clinical evidence of a tissue reaction in the form of fever and malaise was present. Several men in whom striking electrocardiographic abnormalities were demonstrable for several weeks felt perfectly well.

Certain aspects of these cases deserve comment. A true latent period following the acute illness was observed in only 6 of these 20 cases. In this small group the erythrocyte sedimentation rate returned to normal, and the patients were clinically well; later the sedimentation rate became more rapid, and the electrocardiogram, previously normal, was discovered to be abnormal. In the other cases, the sedimentation rate remained above 30 mm. per hour after the initial illness, and frequently the patients presented clinical evidence of continuing disease. Electrocardiograms were obtained for 10 of these patients on the seventh to ninth days of illness and were found to be abnormal in 8. In several these changes persisted for two or three weeks. It is clear, therefore, that a latent period is usually absent when carditis of this type follows acute streptococcic sore throat and that evidence of the presence of carditis may be demonstrated soon after the termination of the acute initial illness.

Bacteriologic and, in 1 case, clinical evidence of reinfection by a new type of group A hemolytic streptococcus was discovered in 7 of these persons. In 1 this event occurred early in the illness; in the others, late. Among the latter were 4 of the 6 patients during whose illnesses a true latent period occurred. Study of 3 of these was sufficiently detailed to indicate that the termination of the quiescent period, with the appearance of an elevated sedimentation rate and carditis, was intimately associated with the reinfection.

In none of these persons did physical signs of pericarditis or endocarditis develop, but the period of observation was too short to exclude the possibility that valvular damage might occur.

THE FACTOR OF REINFECTION

In previous sections of this report it has been suggested that reinfection by a new type[6] of hemolytic streptococci may be of importance in the causation of nonsuppurative complications following hemolytic streptococcus sore throat. Further information on this point can be obtained by determining the incidence of these complications in the whole study group. These data are presented in the table.

Infection by only one type of hemolytic streptococci was demonstrated in 230 patients.

6. Emphasis has been placed on reinfection by a type of streptococcus different from that causing the initial disease, since evidence exists (Kuttner, A. G., and Krumwiede, E.: Observations on the Epidemiology of Streptococcal Pharyngitis and the Relation of Streptococcal Carriers to the Occurrence of Outbreaks, J. Clin. Investigation **23**:139, 1944) that a considerable type-specific immunity persists after recovery from hemolytic streptococcus infection. Relapse, if it can occur, should be equally effective in initiating the phenomenon of the poststreptococcic state.

A continuing disease, with or without carditis, followed the initial illness in 13.1 per cent of these patients, and rheumatic fever followed in 2.6 per cent. Two types were present in the throat during the initial acute illness in 16, and the frequency of complications was similar to that just described.

A new type was discovered to be present in large numbers in the throats of 38 patients two to three weeks after the onset of the initial illness. Continuing clinical disease, with or without carditis, was present in 22.6 per cent of these patients, and rheumatic fever was present in 5.3 per cent—an incidence approximately twice as great as that just described.

Definite clinical as well as bacteriologic evidence of a reinfection by one or more new types of streptococci was obtained in 12 cases. In 3, or 25 per cent, rheumatic fever developed; in 4, or 35 per cent, a severe clinically evident continuing disease, in 1 instance with carditis.

It is clear, on the basis of these observations, that rheumatic fever is but one manifestation of a pathologic process instituted by infection with hemolytic streptococci. Certain patients after such an infection present only signs of continuing tissue reaction in the form of a prolonged erythrocyte sedimentation rate for several weeks; in others this sign is associated with fever, malaise, loss of weight and other clinical signs of an active disease process. Electrocardiographic evidence of carditis may be discovered in a third group of patients showing signs similar to those just described. Finally, arthritis will be observed in a few instances, some of the patients having a mild disease with low grade fever and others a severe illness with signs of pericarditis, endocarditis and the other manifestations of typical rheumatic fever.

It seems impossible to establish adequate criteria for the accurate division of these various late complications of streptococcic disease into separate groups. Carditis with and carditis without arthritis must be regarded as comparable disorders and both appear to be related to arthritic disease without carditis. Since arthritis has been demonstrated without carditis and carditis has been demonstrated without arthritis, there appears to be no valid reason for concluding that examples of continuing disease in the absence of both of these clinical phenomena are unrelated to the first two types of disorder.

Relation of Reinfection by a New Type of Group A Hemolytic Streptococci to the Incidence of Nonsuppurative Poststreptococcic Complications

	Continuing Disease		Continuing Disease and Carditis		Rheumatic Fever		Total Cases with Serial Electrocardiograms	Total Cases		Total with Complications
	Number	Percentage	Number	Percentage	Number	Percentage		Number	Percentage	Percentage
Monotype infections	10	4.3	12	8.8	6	2.6	136	230	77.8	15.7
Early reinfection	0	0.0	1	11.0	1	6.2	9	16	5.4	17.2
Late reinfection, bacteriologic	1	2.6	6	20.0	2	5.3	30	38	12.8	27.9
Late reinfection, bacteriologic and clinical	3	25.0	1	10.0	3	25.0	10	12	4.0	60.0
Total complications	14	4.7	20	10.8	12	4.1	185	296	100.0	19.6

Serious late complications occurred in 60 per cent of this small group of cases.

It is obvious that the numbers of cases are too small to permit accurate statistical analysis. Nevertheless, the increased frequency of nonsuppurative disorders in patients in whom evidence of reinfection by a new type of hemolytic streptococci was discovered suggests that this event may be causally related to the development of these complications.

COMMENT

The study just described of a large number of persons suffering from various types of illness of the respiratory tract indicates that the syndrome known as rheumatic fever occurs only as a sequel to infection by group A hemolytic streptococci. This is in accord with previous information obtained indirectly but appears to be more definitive. One objection to the general acceptance of this etiologic relationship in the past has been the fact that hemolytic streptococcic respiratory disease was extremely common but that rheumatic fever was a rare complication.

Because of these difficulties and because evidence of carditis, the most serious complication, was observed most frequently in the absence of arthritis, it would seem to be desirable to discourage the emphasis placed on the rheumatic fever syndrome and to begin to think in terms of the complications occurring after streptococcic infection, which might well be grouped under the term, "poststreptococcic state." Such disorders as rheumatic fever, postscarlatinal arthritis and atypical rheumatic fever could be considered as a single entity. Furthermore, the fact that serious nonarthritic complications may follow streptococcic infections would be emphasized.

These observations, though more detailed, are in accord with the concept developed over the last thirty years that nonsuppurative disease [7] associated with fever, arthritis, adenitis, nephritis and other signs and symptoms may be a sequel to hemolytic streptococcic infection.

Unfortunately, this study has not determined whether poststreptococcic carditis in the absence of arthritis may lead to valvular heart disease. The close similarity between such cases of carditis alone and cases of carditis with arthritis suggests that it would, particularly if repeated similar episodes should occur in any patient. It should also be emphasized that previous studies of rheumatic fever have shown that the physical signs indicating the presence of a lesion of the cardiac valves may not appear for many months, although electrocardiographic and clinical evidence of carditis may be demonstrated early in the disease.

The precise mechanism involved in the development of these late streptococcic complications, particularly of rheumatic fever, has been a matter of speculation for many years. The most widely accepted suggestion proposes that products of the hemolytic streptococcus are distributed widely throughout the body at the time of the acute infection, becoming "fixed" in various tissues. Later, as antibodies develop as the result of infection, an antigen-antibody combination occurs on the cell surfaces, exciting the rheumatic syndrome and presumably the other nonsuppurative complications of streptococcic disease.[8] This rather simple hypothesis has been modified by Swift and others to include a factor of chronic streptococcic infection on the basis of faulty immunity as essential to the development of hypersensitivity of the tissues.[9]

Such a process, rather analogous to serum sickness, presupposes that a single infection by hemolytic streptococci may establish the pathologic condition. Little actual evidence is available in support of this view. The fact that rheumatic fever rarely occurs in children less than 3 years old although streptococcic disease is common in that age group suggests that the primary infection by these organisms may be incapable of inducing the phenomenon of the poststreptococcic state. Bearg, Boisvert, Darrow, Powers and Trask [10] have emphasized the fact that the tissue reaction to streptococcic infection is altered by the initial infection in children, and Schlesinger [1b] has suggested that repeated infection by hemolytic streptococci may be necessary for the development of rheumatic fever.

This study has further altered the older concept by showing that a true latent period is uncommon in instances of carditis and rheumatic fever and that when it is demonstrated reinfection by a new type of streptococcus has frequently occurred. Electrocardiographic evidence of carditis not only was observed long before the appearance of arthritis but was frequently present soon after the end of the acute suppurative phase of the disease. It therefore seems clear that some phases of the tissue reaction involved in the rheumatic or poststreptococcic state begin early in the so-called latent period, suggesting that a direct toxic action of the products of the streptococcus on the involved structures may be responsible for these disorders. This seems unlikely, however, when it is considered that 80 per cent of all infected persons, including many of the most seriously ill, escape these late complications.

Furthermore, suggestive evidence has been presented which indicates that repeated, closely spaced infections by different types of group A streptococci are more likely to incite late nonsuppurative complications than is a single infection. It seems desirable, therefore, to return to and modify the original concept that these pathologic processes are the result of an antigen-antibody reaction. This is particularly appropriate since recent studies by Rich and Gregory have demonstrated that microscopic lesions similar to those observed in rheumatic fever may be reproduced in rabbits by the production of serum sickness in these animals.

Because reinfection with new types of hemolytic streptococci frequently preceded rheumatic fever and continuing disease, an attractive hypothesis presents itself.

It may be supposed that these late complications occur in patients who have suffered previous streptococcic infection and whose tissues have been sensitized to some fraction or product of the hemolytic streptococcus by antibodies developed at that time. Subsequent infection

7. Keefer, C. S.: The Late Non-Suppurative Disorders of Hemolytic Streptococcal Diseases, Texas State J. Med. **35**:457, 1939.

8. (*a*) Schlesinger.[1b] (*b*) Swift, H. F.: Rheumatic Fever, J. A. M. A. **92**:2071 (June 22) 1929.

9. Swift, H. F., and McEwen, C.: Rheumatic Fever, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1938. Coburn, A. F.: Observations on the Mechanism of Rheumatic Fever, Lancet **2**:1025, 1936.

10. Bearg, P. A.; Boisvert, P. J.; Darrow, D. C.: Powers, G. F., and Trask, J. D.: "Streptococcosis" and "Streptococcic Fever," Am. J. Dis. Child. **62**:431 (Aug.) 1941.

11. Rich, A. R., and Gregory, J. E.: Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**:239, 1943.

would then find the tissues in a hyperreactive state, and the syndromes of the poststreptococcic state could be established. This hypothesis is in accord with the known facts that horse serum sickness in human beings who have received a previous injection of similar serum is more severe and appears in an accelerated form. The presence of carditis early in the latent period and the explosive appearance of arthritis twenty-four to forty-eight hours after the last of repeated streptococcic infections of the respiratory tract could be readily explained on this basis. It is not entirely clear why arthritis followed the first demonstrable carditis at such a long interval in certain cases.

It is possible that a degree of sensitivity of the tissues adequate to permit the development of rheumatic fever is usually obtained only by repeated, closely spaced infections. Evidence of such reinfection was obtained in 6 tof 12 patients exhibiting this syndrome, and in 3 two reinfections occurred. In another study, by van Ravenswaay,[12] the type of streptococcus causing the initial illness was determined for 36 persons in whom rheumatic fever subsequently developed. At that time, a type different from that originally present was discovered in the throats of 28.

While the nonarthritic complications of streptococcic disease frequently, and arthritis occasionally, followed single infections, it is probable that all these men had suffered from previous unrecognized streptococcic respiratory infections, although no evidence can be presented to prove that the infections had occurred. In two arthritic patients, a past history of rheumatic fever suggested that an abnormal sensitivity of the tissues to the products of the streptococcus had been previously established.

The fact that some type of nonsuppurative complication failed to develop in all persons in whom bacteriologic evidence of reinfection was obtained may have been due to an inadequate sensitivity of the tissues and to a necessity for further reinfections. These causes appeared to be factors in 2 cases. It must also be borne in mind that a tissue reaction does not invariably occur when a new type of streptococcus gains lodgment in the throat—a fact that is emphasized by the high incidence of complications in the small group in whom definite clinical reinfection took place.

If it be assumed, as this study indicates, that the arthritic phase of the poststreptococcic state is a special reaction based on extreme hypersensitivity often associated with repeated reinfection, the notable discrepancies between the reported incidence of chronic rheumatic heart disease and of clinical rheumatic fever can be explained. Reinfection may occur on enough occasions in certain areas to excite the development of heart disease but not of arthritis. In other areas, in which streptococcic disease is much more common, reinfection would be a sufficiently frequent event to permit the appearance of rheumatic fever.

The supposed individual resistance to rheumatic fever may be more apparent than real, because it is possible that repeated infection by hemolytic streptococci at suitable intervals will incite the rheumatic process in many, if not all, persons. The rarity of this disease may be explained by the fact that many persons are resistant to infection by these organisms and that others escape the frequent reinfections necessary to induce, in them, a sufficiently great sensitivity of the tissues.

In summary, it seems not unreasonable, on the basis of these observations, to make the following assumptions as the basis for further investigation: (1) that rheumatic fever is invariably induced by infection by group A hemolytic streptococci, (2) that this syndrome is but a part of the whole complex involved in the poststreptococcic state, (3) that these clinical manifestations are the result of altered sensitivity of the tissues to products of the hemolytic streptococcus and (4) that repeated infection with different types of hemolytic streptococci may be necessary for the development of these disorders.

If this working hypothesis is acceptable, then the following statements appear to be correct: (1) that sensitivity of the tissues must occur to some fraction or product of the hemolytic streptococcus and (2) that this fraction or product must be common to all types of group A streptococci.

It would seem desirable, therefore, to obtain these substances in highly purified form and to determine whether they have induced the formation of circulating antibodies and whether the tissues of rheumatic persons are sensitive to them. Similar studies in the past have contributed interesting and suggestive information but the crude nature of the test substances and the failure to perform quantitative studies have lessened their importance.

Such investigation might lead to technics which would permit the determination of dangerous streptococcic hypersensitivity and to possible preventive or therapeutic measures.

12. Van Ravenswaay, A. C.: The Geographic Distribution of Hemolytic Streptococci: Relationship to the Incidence of Rheumatic Fever, J. A. M. A. **126**: 486 (Oct. 21) 1944.

CHARACTERISTIC VASCULAR PATTERN IN PATIENTS WITH RHEUMATOID ARTHRITIS

MEYER NAIDE,* M.D.; ANN SAYEN,* AND BERNARD I. COMROE,†‡ M.D.
PHILADELPHIA

During the grading of the basal vascular tone [1] of normal persons and patients with various diseases by a method recently described by two of us,[2] it was found that patients with rheumatoid arthritis had a characteristic basal vascular tone which explained certain clinical features of the disease. In some patients the diagnosis of rheumatoid arthritis first suggested itself by a characteristic vascular behavior, a dissociated response between the affected and the unaffected digits not ordinarily seen where there is no arterial occlusion.

Since there was no objective information as to the grade of tone in the peripheral vessels of patients with rheumatoid arthritis, the vascular responses of a group of such patients were studied by the method described in this paper.

It is significant that in all the patients with rheumatoid arthritis subsequently studied there was a consistently high grade of basal vascular tone in contrast to that of a large group of normal persons tested, in whom a wide range of low and high vascular tone was found.

Vasospasm appears to be a predisposing factor in this condition—a fundamental vascular pattern, which, together with heredity, susceptibility to infection, chilling and other factors, permits the development of rheumatoid arthritis. It seems more than coincidental that this condition usually is first manifested at the site of greatest vascular tone, namely the digits, and it is suggested that treatment such as that given in other vasospastic disorders, in which emphasis is directed toward vasodilation by interruption of hyperactive vasoconstrictor reflexes by paravertebral block or by caudal anesthesia, may be of benefit for these patients.

Other studies on the capillaries and on the periarticular tissues of patients with rheumatoid arthritis have given conflicting information as to what vascular responses are typical in this condition. Unlike ours, these studies were not done under basal conditions and were primarily concerned with the affected extremities. However, these conflicting observations can be correlated when their relation to our study is considered. Our observation of a high grade of vascular tone in the less affected extremities together with vasodilatation in the extremities in which the arthritic process is active brings into focus the contradictory views on this aspect of the condition obtained from previous observations of the circulation in these patients.

METHOD

The method for grading vascular tone has been described in detail in a recent report.[2] Briefly, this is done by determining the degree of vasoconstriction and vasodilatation, as reflected in temperatures of the fingers and toes, during a cool period and during the application of moderate heat to the trunk in a constant temperature room at 20 C. Reflex heat is applied by means of electric pads set at moderate heat and two blankets. The patient is unclothed except for a light hospital gown and is under basal conditions, having omitted the meal before the test and any medication or hot bath. If the fingers cool rapidly, falling below 25 C. fifteen minutes after the start of the test, and if vasodilation with reflex heat is difficult, the person has a high grade of vascular tone, or is vasospastic. If the fingers cool slowly or not at all, remaining above 25 C. fifteen minutes after the start of the test, the person has a low grade of vascular tone. This method has enabled us to determine the basal vascular tone of over 400 persons (normal persons and patients with rheumatoid arthritis and other diseases). For the purpose of this study the basal vascular tone of 15 patients with rheumatoid arthritis was determined. The ages of the 15 patients varied from 14 to 65 years. Thirteen were females, and 2 were males. The duration of the arthritic process varied from six months to thirty-two years. All the patients were ambulatory.

The type of vascular tone in the rheumatoid arthritic patients was based on the vascular response in the uninvolved or less involved digits and led to the interesting observation that there was in some persons a different or dissociated response in the involved and the uninvolved digits.

† Dr. Comroe died Sept. 14, 1945.

* From the Peripheral Vascular Section of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

‡ From the Arthritis Clinic, Medical Clinic, Hospital of the University of Pennsylvania.

1. Vascular tone is the ability of blood vessels to constrict and to dilate.

2. Naide, M., and Sayen, A.: A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases with Special Reference to the Etiology and Prevention of Thrombophlebitis, Am. J. M. Sc. **207**: 606 (May) 1944.

RESULTS

Two significant observations emerged from this study of vascular tone in patients with rheumatoid arthritis. First, 14 of these 15 patients proved to have a high grade of basal vascular tone. The fifteenth patient had definite involvement of all of the digits, so that the basal vascular tone could not be obtained. In the 14 rheumatoid arthritic patients in whom the basal vascular tone could be determined, the temperature in the fingers fell rapidly in the temperature-controlled room or was already low at the start of the test. The responses of digital temperature of these patients was such as to label them the vasospastic type. Second, there was a "dissociated" vascular response of uninvolved and involved digits, which first suggested the diagnosis of early rheumatoid arthritis in 2 patients, which was later confirmed by roentgenograms, studies of the sedimentation rate and the subsequent clinical courses.

Whereas in most persons vasoconstriction and vasodilatation occur in the toes of both feet or in the fingers of both hands almost simultaneously, in some of the patients with rheumatoid arthritis the processes occurred in a different manner; a finger or toe involved by the arthritic process (early as well as late) usually remained warm longer during the cool period than did an uninvolved digit. When a large joint was involved, the digits of that extremity did not vasoconstrict as easily as did the digits in the opposite extremity if the latter was unaffected or affected to a lesser degree. Furthermore, the vessels of an affected part frequently dilated more readily with reflex heat. The arthritic process, probably as a result of inflammation, seemed to cause vascular relaxation to a greater degree in the affected digits. Observation of this dissociation led to the diagnosis of early rheumatoid arthritis in the 2 patients just mentioned, who were at first suspected of having a vascular condition resembling acrocyanosis, or Raynaud's disease. The diagnosis of rheumatoid arthritis suggested by observation of this dissociated response during the test for vascular tone was later confirmed.

Several other conditions may also give such a dissociated response during the test for vascular tone. These are usually readily differentiated from rheumatoid arthritis. They include hemiplegia, pressure on the brachial plexus by cervical rib, and pressure seen in scalenus anticus syndrome.

One other observation made in this study was that there was much more frequent and a much greater degree of perspiration in the distal phalanges of both hands and feet during the heating period of the test for vascular tone in patients with rheumatoid arthritis than in normal persons.

COMMENT

Relation of Observations to Possible Cause of Rheumatoid Arthritis.—From a study of the vascular tone of these patients with rheumatoid arthritis, the response was such as to indicate that they were in the vasospastic group before this disease developed. The high grade of vascular tone was found in uninvolved digits or extremities. The vessels in the extremities involved by the rheumatoid arthritic process were not as vasospastic as those in unaffected extremities.

We do not yet know all of the factors that may influence vascular tone or why certain persons fall into the group with low vascular tone and others into the group with high vascular tone. The term "vasomotor tone" is not used here, because the tone of blood vessels not only is influenced by the sympathetic nervous system but depends in part on the intrinsic tone of the wall of the blood vessel itself, on pressor substances and on other factors. In many persons sympathetic tone is the predominant factor in determining the grade of vascular tone. The presence of larger than average pupils, measured with a pupillometer in a constant source of light, in patients with rheumatoid arthritis suggests that increased sympathetic tone accounts for the high vascular tone as well as for the increased sweating in these patients.

All persons are subjected to vasoconstriction in the winter, but there is a more prolonged and intense vasoconstriction in vasospastic persons, who respond so readily to cold. The patient with high vascular tone will respond by vasoconstriction more readily than others to emotional stimuli and pain as well as to cold. The higher the vascular tone in a person, the shorter is the duration of vasodilatation following the application of heat. Grant, Mudd and Goldman [3] found that in human beings chilling of the body surface causes vasoconstriction and ischemia in the mucous membranes of the palate, pharynx and palatine tonsils. They also found that chilling of the body results in proliferation of organisms present in the mouth and in the production of sore throats and slight constitutional symptoms. Since the vessels of persons with a high grade of vascular tone constrict more readily to cold, it would appear that patients with rheu-

3. Grant, S.; Mudd, S., and Goldman, A.: A Further Experimental Study on Excitation of Infections of the Throat, J. Exper. Med. **32**:87 (July) 1920.

matoid arthritis who have this tendency may be likely to have infections of the upper respiratory tract more frequently than persons with a low grade of vascular tone. Vasospasm appears to be a predisposing background for rheumatoid arthritis. It is conceivable that without this underlying factor in such patients, rheumatoid arthritis might not develop.

Freyberg and his associates,[4] in a study of 25 patients with rheumatoid arthritis and controls, found that emotional stress produced a drop in skin temperatures indicative of a change in circulation. The differences noted were suggestive but were not conclusive. They concluded that the significance of emotional stress appeared worthy of further investigation in rheumatoid arthritis. Our studies indicate that if a large number of their control subjects were in the normal vasospastic group, one then would not expect significant differences between this group and their patients with rheumatoid arthritis. Had their controls been persons with a low grade of vascular tone, there would have been a significant difference in response between them and the patients with rheumatoid arthritis.

Myers[5] noted that no vasoconstriction was found in the periarticular tissues in persons with rheumatoid arthritis. This observation agrees with our observations of relaxed vessels in involved digits and extremities.

Kovacs, Wright and Duryee[6] observed a noticeable diminution in the volume of the peripheral circulation with a great reduction in the number of capillaries in the peripheral tissues in patients with rheumatoid arthritis. The thin, shiny, atrophic skin with cold, pale, clammy hands and feet and the cutaneous pigmentation in persons with rheumatoid arthritis results from an impairment of circulation; however, this deficiency must be contrasted sharply with the greatly increased blood supply in the articular tissues. Although the extremities are usually cold and clammy, the affected joints may show an increase in local heat.

Hench[7] was unable to find any consistent alteration in the size of the capillaries or in capillary flow in a large number of cases of rheumatoid arthritis and degenerative diseases. Furthermore, it is known that rheumatoid arthritis is not more common in extremities with organic arterial occlusion. Conclusions drawn from patients with organic arterial disease as to the influence of circulation on arthritis are valueless. The effect of vascular spasm differs completely from that of simple arterial occlusion. Not only the arteries but also the veins are involved in the spasm.

It is definitely known that veins can constrict and frequently do so. For example, in thrombophlebitis a paravertebral block is done to relax venospasm as well as arterial spasm. Any obstruction to venous return, whether this is due to an obstruction of veins or to venous spasm, may result in edema. There is scanty information concerning the flow of venous blood in the proximity of joints in rheumatoid arthritis. The patient with rheumatoid arthritis is a vasospastic person, and in many persons the veins as well as the arteries participate in the vasoconstriction. An increase in venous tone outside the area of the inflamed joint in the presence of decreased arteriolar tone secondary to local inflammation in the proximity of joints could result in swelling in that region. Local inflammatory vasodilatation might predispose to local edema in the vicinity of affected joints in the presence of a generalized peripheral vasospasm.

Relation of Observations to Clinical Picture of Rheumatoid Arthritis.—The observation that a high grade of vascular tone is a basic vascular state in patients with rheumatoid arthritis may explain certain clinical features of the disease. The frequent presence of cold hands and feet, increased sweating, symptomatic improvement with vasodilating procedures and perhaps aggravation of the disease by emotional upsets or stress can be readily explained on the basis of a high grade of vascular tone. The blood vessels of normal persons with high basal vascular tone constrict readily to cold and emotional strain. These persons have cold feet and, often, cold hands. They usually sweat more easily, either because of increased sympathetic tone or because of decreased ability to eliminate heat through vasodilatation.

If one tells a normal person with a high basal vascular tone that he is to have an injection, there occurs an immediate drop of 2 to 6 degrees (centigrade) in finger temperature, with a considerable reduction in peripheral blood flow. This behavior is equally characteristic of a

4. Patterson, R. M.; Craig, J. B.; Waggoner, R. W., and Freyberg, R. H.: A Psychosomatic Study of Rheumatoid Arthritis, Univ. Hosp. Bull., Ann Arbor **8**:86 (Oct.) 1942.

5. Myers, W. K.: Etiology of Rheumatoid (Atrophic) Arthritis, M. Ann. District of Columbia **5**:203 (July) 1936.

6. Kovacs, J.; Wright, I. S., and Duryee, A. W.: Surface Temperature and Minute Vessels of Skin in Arthritis, J. A. M. A. **100**:1018 (April 1) 1933.

7. Hench, P. S., in discussion on Kovacs, J.: The Peripheral Blood Circulation in Chronic Arthritis and the Influence of Vasodilators, J. A. M. A. **103**:1804 (Dec. 8) 1934.

patient with rheumatoid arthritis who also has a high basal vascular tone. The high basal vascular tone in patients with rheumatoid arthritis is not abnormally high. It is simply the grade of vascular tone which is found in from 30 to 40 per cent of normal persons.

In testing over 400 subjects without rheumatoid arthritis, increased vascular tone was found much more commonly in women than in men. Clinically there are many more women than men who give a history of cold hands and feet. It is interesting and perhaps significant that rheumatoid arthritis occurs from two and a half to four times as frequently in women as in men and that the occurrence of rheumatoid arthritis is most frequent in the fingers and toes, the sites of greatest vascular tone in the body. These are the sites selected by other conditions associated with vasospasm, namely, Raynaud's disease and scleroderma. Rheumatoid arthritis is more common in cold countries, where vasoconstriction would be expected, and is much less frequent in warm regions, where vasodilatation is the normal state. Changes in barometric pressure may also influence the vascular tone as well as other factors, such as marked variations in temperature.

Relation of Observations to Treatment of Rheumatoid Arthritis.—Our observations suggest that frequent and persistent attempts to produce reflex vasodilatation, as with warm tub baths and by heating the trunk, may tend to relax the tone of peripheral vessels. Repeated lumbar paravertebral block with procaine hydrochloride may prove to be worth while for some patients with persistently painful joints in the lower extremities. Periods of continuous caudal anesthesia for persistent articular pains in the lower extremities may be useful for prolonged vasodilatation and analgesia. The symptomatic benefit obtained by some patients with rheumatoid arthritis from a constant warm, dry climate might be explained on the basis of constant peripheral vasodilatation. Ghormley and Silverglade [8] have stressed the efficiency of systemic heating in contrast to local heating in producing generalized vasodilatation. Also, since these persons are chilled easily, the necessity of proper clothing in cold weather must be stressed.

SUMMARY

A study of the vascular responses of patients with rheumatoid arthritis under basal conditions disclosed a characteristic vascular pattern. The basal vascular tone in these patients is high. Their peripheral vessels are easily constricted. This high vascular tone may explain certain clinical features of the disease and may be one of the basic factors in predisposing persons to rheumatoid arthritis and to flare-ups of the condition after emotional upsets and exposure to cold. It may also explain the causalgia-like symptoms such as hyperesthesia and severe burning pain and a lower threshold for pain, which would maintain a reflex cycle of pain and vasoconstriction.

A characteristic dissociated type of response during the test for vascular tone has permitted early diagnosis of rheumatoid arthritis in some patients.

8. Ghormley, J. W., and Silverglade, A.: Circulation of Joints of Chronic Arthritis, New York State J. Med. **39**:1489 (Aug. 1) 1939.

GALLBLADDER DYE (IODOPHTHALEIN SODIUM)

EFFECT OF INTRAVENOUS INJECTIONS ON CORONARY FLOW, BLOOD PRESSURE AND BLOOD COAGULATION

FLORENCE E. LAWSON, M.D.
CHICAGO

The dangers of intravenous cholecystography have been cited in the literature since 1925. At this time, Graham, Cole and Copher [1] noted the incidence and symptoms of various disturbances occurring in connection with the use of intravenous injections of gallbladder dye.

Palmer and Ferguson,[2] in 1933, reviewed the literature on reactions and contraindications to intravenous cholecystography. Their conclusion was that the chief contraindications are cardiovascular (cardiac decompensation and angina pectoris or coronary sclerosis). In 1938, Lutz and Seyfried [3] published an article on corroboration by autopsy of a clinical diagnosis of sudden heart failure in the presence of coronary sclerosis in a 68 year old man who had been given gallbladder dye intravenously a few minutes before death. The conclusion of Lutz and Seyfried was that intravenous cholecystography is contraindicated in hypertonia and hypotonia and in every case in which there is the slightest suspicion of coronary insufficiency or impending coronary spasm.

In 1939, Guignard and Nemours-Auguste [4] reported an occurrence of syncope, with disappearance of the pulse and loss of urine and feces, following intravenous cholecystography.

It is the purpose of this paper to present 2 cases of anaphylactic shock without coronary occlusion and 2 cases in which coronary occlusion occurred after administration of iodophthalein sodium. I also present the result of my experiments with the drug on both dogs and human beings.

Fig. 1.—Effect of intravenous injection of iodophthalein sodium on coronary flow and blood pressure in the dog.

REPORT OF CASES

1. *Anaphylactic shock from intravenous injections of iodophthalein sodium.*

CASE 1.—F. W. was a 45 year old man with known gastrointestinal allergy. After being given 1 cc. of the gallbladder dye (3 Gm. diluted with 50 cc. of isotonic solution of sodium chloride), he noted a feeling of warmth in his arms, tinnitus and pounding in his head and became unconscious. His pulse was so weak that it was indiscernible, and the blood pressure could not

1. Graham, E. A.; Cole, W. H., and Copher, G. H.: Cholecystography: The Use of Sodium Tetraiodophenolphthalein, J. A. M. A. **84**:1175-1177 (April 18) 1925.

2. Palmer, W. L., and Ferguson, A. N.: Intravenous Cholecystography: Reactions and Contraindications, Tr. A. Am. Physicians **48**:385-397, 1933.

3. Lutz, W., and Seyfried, H.: Gefahren der intravenösen Cholezystographie, München. med. Wchnschr. **85**:1019-1020 (July 8) 1938.

4. Guignard and Nemours-Auguste: Accident grave à la suite d'une injection intraveineuse de tétraiode, Arch. d. mal. de l'app. digestif **29**:211-213 (Feb.) 1939.

be detected. The patient was given 1 cc. of 1:1,000 solution of epinephrine hydrochloride subcutaneously and placed in the Trendelenburg position. After he regained consciousness, his blood pressure was 108 systolic and 80 diastolic. He complained immediately of substernal pain, which persisted in spite of an intravenous injection of a solution of 3¾ grains (0.24 Gm.) of theophylline ethylenediamine. Twenty-four hours later, his blood pressure was 132 systolic and 80 diastolic, and forty-eight hours later it was 140 systolic and 84 diastolic. Serial electrocardiograms showed no diagnostic deformities.

CASE 2.—B. G. was a 40 year old woman with no history of allergy, who immediately after injection of the dye presented a picture of shock. The pulse was thin and thready; she did not respond to external stimuli, and the blood pressure could not be detected. Epinephrine, in addition to the usual shock therapy, was given, and she responded. She did not complain of thoracic pain.

TABLE 1.—*Effects of Intravenous Injections of Iodophthalein Sodium on Dogs*

	Coronary Flow Cc.	Blood Pressure	Pulse Rate
Dog 1. Weight 11.6 Kg.			
Control	0.54	3.1/2.7	144
50 seconds after 500 mg. dye	1.17	2.4/2.0	150
Dog 2. Weight 10 Kg.			
Control	1.26	5.7/5.4	123
50 seconds after 500 mg. dye	2.70	4.1/3.6	123
Control	1.62	5.2/4.7	114
25 seconds after 250 mg. dye	2.52	4.1/3.6	123
Control	1.80	4.7/4.2	120
30 seconds after 175 mg. dye	2.16	4.5/4.0	120
Dog 3. Weight 8.2 Kg.			
Control	0.54	2.0/1.7	111
20 seconds after 500 mg. dye	1.44	1.4/1.0	105
Dog 4. Weight 9 Kg.			
Control	1.62	5.0/3.8	117
35 seconds after 460 mg. dye	2.68	3.0/2.6	102
Control	1.17	3.4/3.2	99
55 seconds after 230 mg. dye	1.80	2.9/2.5	90
Control	1.44	2.3/1.8	93
50 seconds after 115 mg. dye	2.25	2.2/1.7	78
Control	1.89	2.4/2.0	90
50 seconds after 75 mg. dye	2.25	2.35/1.9	99
Control	2.34	2.3/1.95	105
45 seconds after 50 mg. dye	2.70	2.3/1.85	108

2. Coronary occlusion following the intravenous injection of gallbladder dye.

CASE 3 (from Wesley Memorial Hospital, where intravenous cholecystography was employed).—C. A. Y. was a 55 year old man with a history of angina pectoris, who was given an intravenous injection of iodophthalein sodium. Immediately after the dye was given, he had a severe attack of dyspnea, pain in his arms and a feeling of constriction in his chest and of faintness. His blood pressure taken two days previously was 176 systolic and 102 diastolic; but after the gallbladder dye was given, it was 140 systolic and 90 diastolic. Ten minutes later, it had risen to 180 systolic and 110 diastolic. Serial electrocardiograms showed changes in the T wave compatible with infarction. His white blood cell count was 22,400 the day after the dye was injected. His sedimentation rate two days before the dye was given was 20 mm. in one hour; it was 23 mm. the day after injection of the dye. His temperature rose 1 degree above normal the day after the gallbladder dye was given.

3. Coronary occlusion following the oral administration of gallbladder dye.

CASE 4 (from St. Luke's Hospital).—C. H. W. was a 65 year old man who had a history of angina pectoris. He was given gallbladder dye orally and one hour later had an acute coronary occlusion, with a drop in blood pressure from 128 systolic and 102 diastolic to 60 systolic and 30 diastolic. An electrocardiogram indicated an infarction of the posterior wall. The patient died fourteen days later.

EXPERIMENTAL STUDIES

4. Experiment on Dogs.—The Morawitz cannula method of measuring coronary flow was employed. I feel that this method is valuable for judging the comparative result of flow. The dogs were anesthetized

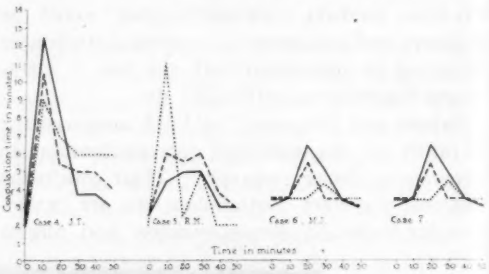

Fig. 2.—Coagulation times of 4 patients after intravenous injections of iodophthalein sodium. Ten milligrams of heparin was injected intravenously before the gallbladder dye was injected (dotted line) as a control, five hours after the gallbladder dye was injected (broken line) and twenty-two hours after the gallbladder dye was injected (solid line).

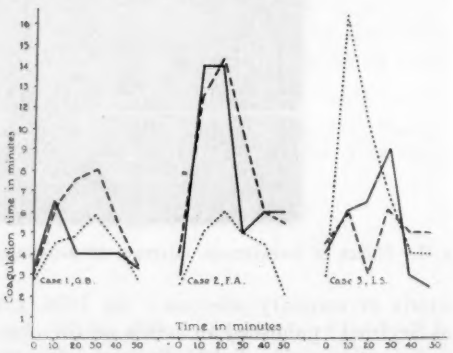

Fig. 3.—Coagulation times of 3 patients after intravenous injections of iodophthalein sodium. Ten milligrams of heparin was injected intravenously before the gallbladder dye was injected (dotted line) as a control, five hours after the gallbladder dye was injected (broken line) and twenty-two hours after the gallbladder dye was injected (solid line).

with dial (5,5-diallylbarbituric acid), 0.6 cc. per kilogram of body weight; an artificial respiration setup was established, and the carotid artery was cannulated for intravenous administration of the drugs used. The dogs were heparinized. The Morawitz cannula was then inserted into the coronary sinus. Iodophthalein sodium was administered intravenously in a dose proportionate to that given human adults, 3 Gm. in 24 cc. of water for a 155 to 160 pound (70 to 73 Kg.) adult. The results are shown in figure 1 and table 1.

The conclusion reached as the result of these experiments on dogs is that the intravenous injection of iodophthalein sodium produces a fall in blood pressure and increases coronary flow.

5. *Experiments on Human Subjects.*—The effect of intravenous injections of iodophthalein sodium on the coagulability of the blood was determined for 7 patients by means of the heparin tolerance test described by de Takáts.[5]

A control heparin tolerance curve was made for each patient before the intravenous injection of gallbladder dye was given. A curve was made at the end of five hours and another at twenty-two hours after the dye was administered. The results of these tests are shown in figures 2 and 3. A summary of the charts shows that, in the 7 patients studied there was prolonged coagulation time in 4, both at five hours and at twenty-two hours after the iodophthalein sodium was administered. In 3, there was a decreased coagulation time, as indicated by the heparin tolerance curve.

Studies of the blood pressure were done prior to the injection of gallbladder dye, immediately after the dye was injected and at five hour and twenty-two hour intervals. There was noted a drop in blood pressure in 5 patients, while 2 patients' pressures remained the same (table 2).

CONCLUSIONS

1. Iodophthalein sodium produces an increase in coronary flow in dogs.

2. Intravenous injections of iodophthalein sodium produce a drop in blood pressure, both in dogs and in human beings.

3. The drop in blood pressure after injection of the intravenous gallbladder dye, observed both in experimental dogs and in human beings, may account for the occurrence of shock noted in patients after injection of the dye. In patients with sclerotic arteries, the drop in blood pressure after intravenous injections of gallbladder dye may produce enough diminution of coronary flow to result in coronary thrombosis.

TABLE 2.—*Readings of Blood Pressure Before and After Intravenous Injections of Iodophthalein Sodium*

Patient	Before Dye	Immediately After Dye	Five Hours After Dye	Twenty-Two Hours After Dye
1. G. B.....	94/64	88/60	106/80	110/70
2. F. A.....	112/68	112/68	112/68	110/64
3. L. S.....	121/86	112/78	100/76	110/78
4. J. T.....	130/85	125/85	106/80	104/76
5. R. M.....	136/86	120/82	138/90	124/84
6. M. J.....	120/78	120/78	120/74	116/78
7.	110/70	110/70	110/74	106/80

4. While the mechanism of the production of coronary accidents by intravenous injections of gallbladder dye in persons with coronary arteriosclerosis is not fully explained by these experiments, it is clear that both blood pressure and coronary blood flow are profoundly affected. Obviously intravenous injections of gallbladder dye are contraindicated in persons with coronary arteriosclerosis.

5. de Takáts, G.: Heparin Tolerance, Surg., Gynec. & Obst. **77**:31-39 (July) 1943.

CHANGES IN THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH ENCEPHALITIS COMPLICATING PNEUMONIA

I. A CLINICAL STUDY

A. B. BAKER, M.D., AND H. H. NORAN, M.D.
MINNEAPOLIS

In view of the extensive literature on the subject of pneumonia, it is surprising that the cerebral complications accompanying or following this disease have been almost entirely neglected. Three important factors probably account for the neglect of the subject of cerebral complications: 1. Pneumonia is usually treated by the internist, who in most cases is not greatly impressed by the milder cerebral symptoms. 2. The pulmonary involvement often overshadows and even covers many of the cerebral symptoms. 3. The great interest in the etiologic factors and the treatment of the pulmonary lesions has almost excluded any investigation of other phases of this illness. The existing literature on this subject, therefore, is comprised largely of isolated case reports published in French and South American journals. Bonaba and his associates,[1] in 1939, were able to collect from the literature but 28 cases of pneumonia encephalitis. Adler,[2] in reviewing 100 cases of postinfectious encephalitis occurring during a ten year period, observed 11 following pneumonia. The total cases of pneumonia during this same period numbered 18,000, making the percentage of cerebral complications but 0.06. When one considers that pneumonia is one of the most common diseases of the human race and that many patients with the disease are treated with but a minimum of medical care, it seems inevitable that many instances of mild or even severe encephalitis are being overlooked regularly and that the frequency of this complication is greater than is generally suspected. Detection of these complications becomes of paramount importance, since, as will be pointed out, severe cerebral residuals may often follow relatively mild pneumonia.

Comby,[3] who first called attention to this most interesting complication, felt that this form of encephalitis is associated more often with bronchopneumonia than with lobar pneumonia. His contention has not been substantiated. As a matter of fact, encephalitis of a nonpurulent nature may follow almost every variety of pneumonia, even the more recently described "virus pneumonia" or virus pneumonia type A (Reimann).[4] The cause of these cerebral lesions is, as yet, unknown. Although most cases reported have occurred during infancy and early childhood, almost every age group may be involved. Generally, however, the nature of the cerebral complications is more dramatic in younger persons, and hence they attract more attention. Pneumonia encephalitis may appear at the beginning of, during or after the pneumonia, frequently appearing during convalescence, after the patient has become afebrile and appears well on the road to recovery. The onset of symptoms is usually abrupt but may be gradual and mild. There is a decided variability of symptoms, ranging from such generalized complaints as headache, vomiting, vertigo and lethargy to the more dramatic complications of coma, convulsions, delirium, monoplegia, hemiplegia, athetosis and psychic disturbances. The most common picture seen is that of an acute meningoencephalitis that appears either at the height of the illness or at the time the acute infectious process is subsiding (Bonaba and co-workers,[5] Reimann,[4] and de Filippi and Fernández[6]). The patient complains of head-

From the Department of Neuropsychiatry, University of Minnesota.

This study was aided by a grant from the University of Minnesota Graduate School.

1. Bonaba, J.; Marcos, J. R., and Mendivil de Agorio, S.: Nuevos casos de encefalitis neumónica, Arch. de pediat. d. Uruguay **12**:317, 1941.

2. Adler, A.: One Hundred Cases of a Condition Diagnosed as Acute Encephalitis, Arch. Neurol. & Psychiat. **44**:541 (Sept.) 1940.

3. Comby, J.: L'encéphalite aiguë chez les enfants, Arch. de méd. d. enf. **10**:577, 1907.

4. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filterable Virus, J. A. M. A. **111**:2377 (Dec. 24) 1938.

5. Bonaba, J.; Boni, E., and Barberouse, C. M.: Tres nuevos casos de encefalitis post-neumónica, Arch. de pediat. d. Uruguay **8**:245, 1937.

6. de Filippi, F., and Fernández, I.: Encefalitis paraneumónica, Arch. argent. de pediat. **11**:22, 1939.

ache, vertigo, vomiting, restlessness and some lethargy. In some cases the lethargy may deepen into coma, while in others the encephalitis may appear suddenly as deep somnolence in a patient who was apparently on the road to recovery (Bonaba and co-workers,[5] de Filippi and Fernández,[6] Nové-Josserand and associates [7] and Gareiso and Sagreras [8]). Bonaba, Marcos and Mendivil de Agorio [1] reported 1 such case, that of a 5 year old child in whom the somnolence appeared before the onset of the pneumonitis. The child was extremely lethargic, revealed bilateral positive toe signs and signs of bilateral papilledema. This type of somnolence at times is associated with motor restlessness and extreme excitation.

In many instances, after a short period of generalized complaints, a severe delirium develops, with a clouded sensorium and even hallucinations (Mollard and Dufourt,[9] Reimann,[4] Eschbach,[10] Stephan,[11] Comby [12] and Navarro [13]). Since this development most frequently occurs during the height of the infectious process, it has been assumed to be due to the toxic state produced by the pyrexia. However, the appearance of a similar picture during convalescence (Navarro [13] and Mollard and Dufourt [9]), as well as the numerous associated neurologic observations, strongly suggest an independent encephalitic process. Mollard and Dufort, for example, reported a case of a 44 year old man who, while recovering from grave pneumonia, suddenly experienced a severe delirium with overactivity, followed by lethargy, stupor, convulsions and death within a period of four days. In Eschbach's patient, the delirium appeared on the fourth day of illness and was accompanied with numerous focal symptoms, such as Kernig's sign, strabismus of the left eye and diplopia. Comby [12] reported the amazing case of a boy 4 years of age. Nine days after the onset of pneumonitis, the patient became delirious and experienced visual hallucinations. After a few days a catatonic state manifested by generalized hypertonicity developed. Although the child seemed quiet and calm, his limbs would remain in peculiar positions, as in typical catalepsy. This patient was observed for only six weeks, but during that time he showed no signs of improvement.

Convulsions of both a focal and a generalized nature have been reported (Stephan,[11] Comby,[12] Eschbach [10] and Garzón [14]). Garzón's patient was a 2½ year old child, who was lethargic and had generalized seizures thirty-six hours after becoming afebrile. The spinal fluid revealed 120 cells, of which 84 per cent were mononuclear leukocytes. The child remained unresponsive, with a spasmodic rigidity of all limbs resembling a decerebrate rigidity. Death ensued in two weeks. Eschbach and Comby reported convulsions of a jacksonian type. In Comby's case, the convulsions were followed by persistent somnolence and paresis of the right side. Stephan studied a dramatic case in which generalized convulsions appeared at the height of the pneumonitis, accompanied with headaches, stiff neck and mild delirium. The convulsions continued for a week, leaving a spasticity of all limbs, particularly the lower, and ptosis and miosis of the right eye. Nine days after the onset of the cerebral involvement, the patient died in a state of respiratory paralysis.

Probably the most impressive of all the cerebral complications is the sudden onset of motor weakness occurring during convalescence and after the patient appears to be recovering (Mouriquand and associates,[15] Lesieur,[16] Regine,[17] Buchanan,[18] Barni,[19] Stephan,[11] Comby [12] and Eschbach [10]). Hemiplegias predominate, although monoplegias (Buchanan) and even quadriplegias (Comby) have been reported. Barni observed a 22 month old child in whom paralysis of the right side associated with aphasia appeared after four days of a normal temperature. Recovery began after nineteen days and was complete in one week. Regine's case was

7. Nové-Josserand, L.; Rougier, and Feuillade: Névraxite consécutive à une pneumonie chez une enfant de 4 ans. Guérison, Lyon méd. **153**:272, 1934.

8. Gareiso, A., and Sagreras, P. O.: Encefalitis agudas en los procesos infecciosos, Rev. argent. de neurol. y psiquiat. **2**:233, 1936.

9. Mollard, J., and Dufourt, A.: Sur l'encéphalite aiguë au cours de la pneumonie, Lyon méd. **66**:821, 1911.

10. Eschbach, H.: Pneumopathies à manifestations cérébro-méningées, Arch. méd.-chir. de Province **27**:47, 1937.

11. Stephan, B. H.: Des paralysies pneumoniques, Rev. de méd., Paris **9**:60, 1889.

12. Comby, M.: Les encéphalitis aiguës post-infectieuses de l'enfance, Thesis, Paris, Masson & Cie, 1935.

13. Navarro, J. C.: Neumonia, encefalitis, absceso de fochier, Prensa méd. argent. **7**:409, 1932.

14. Garzón, W. P.: Meningoencefalitis postneumónica, Med. de los niños **35**:261, 1934.

15. Mouriquand, G.; Bernheim, M., and Boucomont, J.: L'encéphalite aiguë dans la pneumonie infantile, Presse méd. **41**:211, 1933.

16. Lesieur, M. M.; Froment, J., and Garin, C.: Hémiplégie pneumonique et pneumococcie méningée sans réaction leucocytaire du liquide céphalorachidien, Bull. et mém. Soc. méd. d. hôp. de Paris **28**:570, 1909.

17. Regine, A.: Encefalo-mielite nella bronco-polmonite infantile, Riforma med. **50**:667, 1934.

18. Buchanan, D. N.: Repeated Attacks of Hemiplegia with Ataxia and Bulbar Palsy in a Child, Proc. Roy. Soc. Med. **24**:1064, 1930.

19. Barni, B.: Sindrome encefalitica transitoria postneumonica, Riv. sper. di freniat. **12**:31, 934, 1935.

much more dramatic and less favorable. His patient was a 6 year old child, in whom weakness of the right arm and both legs developed after five days of convalescence. Neurologic examination revealed right strabismus and weakness of the right arm with spastic paraplegia of the lower limbs. The patient improved slowly but after forty days suddenly had a recurrence of the pneumonia and died in a state of extreme psychomotor excitement. Buchanan reported neurologic complications persisting over a four year period, indicating a continued action of the pathologic process. At the onset his patient was unconscious for three weeks. After recovery she was blind and dragged her left leg. Periodically during the next four years, this patient had varying neurologic disabilities, which improved only to recur. These consisted of drowsiness, vomiting, tremor of hands, facial weakness and varying monoplegias and hemiplegias. At the time she was last seen, she still revealed a persistent hemiplegia of the right side, with gross ataxia of both arms.

In addition to these more common complications, isolated reports are available indicating a fairly widespread and unpredictable localization of the cerebral pathologic process, producing amauroses (Buchanan [18]), aphasias (Prandi,[20] Bonaba and Cantonnet [21] and Carrau [22]), conjugate deviations (Prandi [20]) and varying types of involvement of the extrapyramidal system (Gareiso and Sagreras,[8] Bernheim and Bonnefoy [23] and Moriquand and associates [15]).

In view of the paucity of reports on this most striking and often most important complication of pneumonia, it was felt that a review of some of our cases might serve the purpose of stimulating more interest in this form of cerebral pneumonia. The possibility of such persistent cerebral complications even in the face of mild pneumonitis makes it imperative that the presence of any involvement of the central nervous system be considered in the ultimate prognosis of any case of pneumonia, particularly when the disease occurs in a child. In selecting our cases we have attempted to use those which demonstrate the various clinical varieties of cerebral involvement.

20. Prandi, G.: Di quattro casi di afasie insorti durante malattie infettive, Pediatria d. med. prat. **10**: 240, 1935.

21. Bonaba, J., and Cantonnet, H.: Neumococias extrapulmonares de la infancia, Arch. de pediat. d. Uruguay **9**:396, 1935.

22. Carrau, A., cited by Bonaba, J., and Barberouse, C. M.: Encefalitis postneumónica, en al niño, An. Fac. de med. de Montevideo **24**:28, 1939.

23. Bernheim and Bonnefoy: Encéphalite aiguë au cours d'une pneumonie infantile, Lyon méd. **152**:335, 1933.

REPORT OF CASES

CASE 1.—N. K., a 10 year old girl, was first taken ill with a mild cough and a slightly elevated temperature. During the next few days her temperature rose to 104 F., and she was hospitalized. Examination revealed rales and scattered areas of dulness in the left side of the chest. Roentgenograms of the lungs showed a peribronchial infiltration in the subclavicular region. Roentgenographic examination four days later showed the process to have extended. The patient continued to be septic for six days, with temperatures ranging from 99 F. to 105 F. No organisms could be cultivated from the sputum, and there was no response to chemotherapy. After six days her temperature gradually returned to normal, and convalescence ensued. Throughout her entire illness the patient remained mentally clear and cooperative.

On the sixth day of convalescence the patient suddenly vomited and became unresponsive. When she did talk, her speech was slurred, and she appeared confused and bewildered. Three days later she began to respond slightly by shaking her head. Throughout this time her temperature remained normal, and she did not appear toxic. Examination three days after the onset of the cerebral symptoms revealed her fundi to be slightly congested. There was a weakness of the right upper and of the left lower extremities, with hyperactive reflexes in the paretic limbs. There was a positive toe sign on the left. Coordination was poor in the left lower limb. All sensation was intact. A spinal puncture showed 20 cells per cubic millimeter, with 90 per cent mononuclear leukocytes.

Improvement continued to be slow. The patient became more alert, and her slurred speech disappeared. She had only a vague recollection of some of the occurrences during her acute illness. After six weeks of convalescence, she was allowed to be up but noticed great difficulty with gait. Neurologic check-up at this time revealed persistent signs. She had difficulty repeating test phrases. She seemed somewhat unstable emotionally, giggling readily and without provocation. There was weakness of the right upper and both lower limbs. The right triceps reflex was greater than the left, while the left ankle and knee jerks were greater than the right. There was a bilateral ankle clonus. The Romberg sign was elicited, and there was a definite ataxic gait. Psychometric examination revealed definite evidence of organic deterioration of the brain. This patient was again examined three months after the acute illness. Her neurologic signs had remained unchanged, except that her ataxia had become somewhat improved. Her gait was unsteady and incoordinated. Psychometric testing still showed evidence of organic deterioration.

Comment.—This case is of extreme significance, since it indicates how dramatically severe complications affecting the nervous system may appear in association with relatively mild and subsiding pneumonia. In this patient, unfortunately, the cerebral damage appears to have been irreversible, so that three months after its onset definite and incapacitating residuals still remained.

CASE 2.—B. R. was a 1 month old girl, in whom four days prior to her hospitalization pneumonia associated with thrush of the nose and throat developed. Her chief symptoms consisted of cough, fever and bubbling rales and rhonchi audible over both lungs. The leuko-

cyte count was normal. Roentgenograms of the chest revealed a pneumonic process. Cultures of materials from the nose and throat failed to disclose a causative organism.

After the first week, the infant's temperature remained normal for three days but thereafter had an intermittent course, usually rising no higher than 102 F. to 103 F. Her cough continued. A mild cyanosis and respiratory difficulty occasionally required administration of oxygen. She soon became lethargic and drowsy and would often fall asleep, even while being attended by the nursing staff. At times the somnolence was pronounced, but the patient could still be aroused. It was also noted that she remained listless and apathetic and even remained asleep during intermittent periods of respiratory distress. The infant's condition became steadily worse, and she died on the twentieth day of her illness.

Autopsy.—There were patchy bronchopneumonia and a multiplicity of small abscesses throughout both lungs. The external surface of the brain showed no discernible abnormalities. On coronal section, a large number of small petechial hemorrhages were observed throughout the subcortical white substance of both cerebral hemispheres. Definite petechiae were not found in either the brain stem or the cerebellum.

Microscopic studies of the brain demonstrated an extremely severe vascular congestion throughout all regions, associated with a prodigious number of petechiae in the cerebral white matter. The petechiae were usually of the ring variety, but ball hemorrhages were not uncommon. Occasionally a capillary was occluded by a typical platelet thrombus. The nerve cells in many regions of the cortex exhibited chromatolysis and swelling.

CASE 3.—Baby H. was a boy born two months prematurely. Since the mother had mild preeclampsia, labor was induced, and delivery occurred without any complication. The child was entirely normal and suffered from no respiratory distress. The Wassermann reaction of the cord was negative. The mother had always been in good health and had one older child, who was living and well.

Examination of the infant revealed no abnormality other than prematurity. His condition progressed favorably for twenty-five days. On the twenty-sixth day, labored and irregular respiration, cough, a low grade fever and leukocytosis developed. Numerous rales were heard bilaterally over the lungs. Roentgenograms of the chest revealed a pneumonic involvement of the upper lobes of both lungs.

The patient's condition improved slowly. The entire course was relatively afebrile, with only occasional elevations of temperature between 100 F. and 101 F. After a period of improvement for fourteen days, the infant became noticeably nervous and apprehensive and frequently refused his feedings. Any disturbance caused a generalized shaking suggestive of convulsive movements. A roentgenogram of the chest four days later demonstrated that considerable resolution had taken place, the left lung being entirely clear. Another roentgenogram of the chest six days later showed only a minimal residual of the consolidation in the upper lobe of the right lung. In spite of this improvement of the pneumonic process, the patient remained irritable and restless. Two weeks after the onset of the neurologic complications and a month after the beginning of the pneumonia, a positive Chvostek sign was noted. Tetany was excluded by a blood calcium value of 11.3 mg. per hundred cubic centimeters. The infant became weak, had an intermittent low grade fever and manifested a generalized trembling of the entire body. Two days later he suddenly lost consciousness; his eyes deviated upward, and he vomited. After this he remained listless, and dysphagia developed. Thereafter he failed rapidly, and he died later that day.

A spinal puncture was performed immediately after death. It revealed a pleocytosis of 189 cells per cubic millimeter, almost all of which were mononuclear leukocytes. The protein content of the spinal fluid was also elevated, being 126 mg. per hundred cubic centimeters.

Autopsy.—There was a congestion of the lower lobes of both lungs. Microscopic study of the lungs demonstrated only mild bronchopneumonia showing resolution. Both the liver and the spleen were slightly enlarged, apparently as a result of chronic congestion. The external examination of the brain showed nothing abnormal.

Microscopic studies of the brain revealed a prominent vascular congestion and an occasional petechial hemorrhage. A few of the larger hemorrhages were rather diffuse. In a few vessels there was a sparse leukocytic infiltration of the adventitia, consisting of a small number of either mononuclear leukocytes or neutrophils or of an admixture of both. A similar sparse exudate was also observed in the leptomeninges in scattered small areas. This was generally associated with a well defined vascular congestion and small extravasations of blood. Nerve cell disease was present in the cortex and consisted mainly of irregular areas of neuronal shrinkage and pyknosis. The Purkinje cells of the cerebellum were swollen and chromatolytic.

Comment.—This illustrates a typical instance of death due to a cerebral complication in the course of a recovering pneumonic process. In spite of the mild course of the original pneumonia and in the absence of severe pyrexia, this patient had cerebral symptoms indicative of a widespread cerebral involvement. The severity of the encephalitis was not influenced by the extent of the precipitating pulmonary involvement, and, as is occasionally the case, the illness terminated fatally after a fairly rapid downhill course.

CASE 4.—E. A., a 45 year old woman, first showed evidence of a pneumonic process two days before her admission to the hospital. She seemed to be progressing fairly well until shortly before her admission, when she suddenly became comatose without exhibiting any other associated symptoms. Examination revealed the patient to be entirely unresponsive. Her pupils were pinpoint-sized and fixed. There were many fine and coarse rales throughout both pulmonary fields. The patient showed no evidence of any motor weakness but did have bilateral positive toe signs. The patellar reflexes were reduced. The Brudzinski sign was slightly positive, but Kernig's sign was not elicited. Examination of the sputum showed a type VIII pneumococcus.

The patient's temperature during the next few days ranged between 99 F. and 101 F. Shortly after her admission a lumbar puncture was performed, and, while the fluid was clear, there was noticeably increased pressure. The patient continued to remain unresponsive and involuntary. Twitchings of her arms and legs developed, and she died after three days of coma.

Autopsy.—There was a pneumonic consolidation of the middle and upper lobes of the right lung, as well as a number of smaller areas of patchy consolidation within the left lung. The external surface of the brain appeared essentially normal. Coronal sections, however,

demonstrated a large number of petechial hemorrhages disseminated throughout the subcortical white matter and basal nuclei of both cerebral hemispheres. A smaller number of petechiae were scattered throughout the cerebellum. The pons and medulla appeared normal.

CASE 5.—E. C., a 50 year old man, was admitted to the hospital with lobar pneumonia. Shortly after the onset of his illness the patient, who had been in good health, had a grave delirium with extreme psychomotor overactivity. His mental involvement necessitated his transfer to the hospital.

At the time of his admission he was found to be acutely ill, with a temperature of 103 F., rapid respiration and slight cyanosis. Although he appeared lethargic, he was extremely restless. He was poorly oriented and at times confused. On the third day of his stay in the hospital he showed evidence of early bilateral papilledema. His temperature rose to 105 F., and he became more irrational. He became extremely restless and at times agitated, wandering from his bed and being very difficult to control. Because of his motor overactivity, restraints were required to keep in him in place. He continued to manifest an extreme delirium, failing rapidly and dying on his fourth day in the hospital.

Although early cultures of the blood showed no growth, a postmortem culture yielded a nonhemolytic Streptococcus.

Autopsy.—The lungs showed an extensive lobar pneumonia in the stage of early resolution. Gross examination of the brain displayed a vascular congestion.

Microscopic sections revealed pronounced vascular congestion and scattered petechiae in the form of small perivascular extravasations and ball hemorrhages. In a few regions, small amounts of blood had escaped into the subarachnoid space. The neurons of the cerebral cortex and those of the nuclei of the cranial nerves showed regressive alterations. While many nerve cells were shrunken and pyknotic, others had undergone swelling and tigrolysis with a few ghost cells resulting. In irregular focal areas the myelin displayed a minimal loss of its tinctorial properties.

Comment.—This case represents an instance of fulminating pneumonia during which the patient showed severe delirium. Although the cerebral complication in this case could be ascribed to the toxicity caused by the pyrexia, it is interesting to note that the cerebral changes were similar to those seen in cases in which no severe toxicity appeared to be present. It is also of interest to note that in this case of apparent streptococcic pneumonia the cerebral changes were similar to those seen in the previously reported cases of pneumococcic and virus pneumonia.

CASE 6.—N. P. was a white man 29 years of age, whose illness began six days before his hospitalization. His early complaints consisted of a nonproductive cough, fever, general malaise and diffuse discomfort in the joints and muscles. On the fifth day of his illness generalized asthenia, severe coughing, excessive sweating, slight lethargy, irritability and a temperature of 104 F. developed.

Examination at the time of his admission revealed diminished breath sounds over the lower lobes of both lungs and a strong suggestion of audible bronchial breathing over the lower portion of the left lung. Mild tympanitis and epigastric tenderness were noted. Although the patient's sensorium seemed to be somewhat clouded, he was able to converse coherently without a sign of confusion. Roentgenograms of the chest demonstrated a bilateral patchy involvement typical of lobular pneumonia.

In spite of moderately large doses of sulfathiazole, the patient remained acutely ill for seven days. On the eighth day his temperature dropped to 99.4 F., and his general condition improved considerably. It appeared as if his recovery had begun. However, within the next twenty-four hours he rather abruptly became stuporous, and complete hemiplegia of the right side with concomitant motor aphasia developed. There also appeared episodes of twitching of the upper and lower limbs on the left, which recurred intermittently at varying intervals for the next few days. A lumbar puncture yielded a clear spinal fluid, which contained a slight increase in protein (59 mg. per hundred cubic centimeters) with no increase in cells.

During the ensuing days his condition steadily improved. His sensorium gradually cleared, but he remained noticeably lethargic. At times he would be restless and irritable, showing evidence of explosive anger. Motor function gradually began to return in his lower limb, but there was no recovery in his upper extremity. His speech also improved, so that after a period of two months most of his conversation could be understood. Even at this time, if the patient became tired or excited, his speech would again become unintelligible. His strength continued to improve, so that at the time of his discharge, two months after the onset of the cerebral complications, he was able to walk unassisted but with a definite limp.

Improvement continued after he left the hospital. One year later, however, he still showed a definite defect of gait and was unable to write with his right hand. He still complained of occasional difficulty in finding the correct words to express himself. His irritability persisted and at times resulted in definite outbursts of temper. He was last examined one and one-half years after his acute illness. He still presented evidence of a mild disturbance of the personality and of slight intellectual deterioration. There were a minimal paresis of the right lower side of the face and a mild weakness of the grip in the right hand. The lower limbs revealed no involvement, although an ankle clonus was elicited on the right. The patient's pronunciation of words was not disturbed; however, he showed considerable difficulty in expressing his thoughts.

Comment.—The sudden onset of the hemiplegia in this case would naturally suggest the possibility of the occurrence of some embolic process. However, when one reviews the observations more carefully, it readily becomes apparent that the involvement was much more widespread and that the hemiplegia was only a single expression of a widely disseminated encephalitic process.

RÉSUMÉ OF CLINICAL OBSERVATIONS

The clinical picture produced by the involvement of the central nervous system in pneumonia is characterized by a noticeable variability from case to case. Judging from a review of the cases reported in the literature as well as from our own studies, we can divide the clinical syn-

dromes generally seen into five relatively independent groups. These divisions are of definite importance, since each seems to carry with it certain characteristics which are of both diagnostic and prognostic significance. Each group, therefore, warrants a brief comment.

1. *Generalized Symptoms of a Nonspecific Nature* (case 1).—The symptoms in this form of the illness are of a general nature and consist of headache, vomiting, diplopia and mild lethargy often interrupted by periods of excitement. These complaints generally appear shortly after the onset of the pulmonary symptoms and disappear after the pneumonic involvement recedes. At times these symptoms may become severe, developing into fairly intense lethargy or severe excitement, or even visual hallucinations. The neurologic examination will reveal scattered signs. Signs of meningeal irritation almost invariably occur during the first few days of the illness, only to be the first of the cerebral symptoms to disappear. The prognosis in this form of illness is generally good. In most cases recovery is complete within two weeks, with no residuals. In only 1 case reported by Reimann[4] was death due to the encephalitic involvement. The changes in the spinal fluid vary from none to a pleocytosis of as high as 270 cells (Reimann). As a rule there is a mild pleocytosis, consisting chiefly of mononuclear leukocytes.

2. *Delirious Form* (case 5).—Often during the height of the pneumonia there is an acute delirium. The onset most often is gradual, the patients becoming apprehensive, restless, bewildered and mildly confused. They may be quiet and muttering or may show a severe psychomotor acceleration with overactivity, visual hallucinations and even occasional catatonic states (Comby[12]). In Navarro's[13] case, the delirium passed into a deep stupor. Neurologically, these patients may show scattered signs, although some are entirely normal. The spinal fluid reveals a pleocytosis in about half the cases. Recovery is the rule and occurs rapidly after a few days of confusion. In some, however, the mental complication may persist for weeks or even months. Comby reported 1 such case, in which the psychotic state persisted as a permanent residual.

3. *Convulsive Type* (case 3).—It is questionable whether this type constitutes a separate form of complications of the central nervous system associated with pneumonia or whether it merely comprises an accompanying symptom of the other forms of cerebral complication. In most of the reported cases, the convulsions occurred independently of any other manifestations and hence have been placed by us as a separate group. The convulsions are usually generalized and appear from four to fifteen days after the pneumonia. Occasionally the convulsions may be focal, resembling a typical jacksonian seizure. They are usually recurrent over a period of days and are followed by periods of lethargy or somnolence. The prognosis is invariably favorable in this type of case, improvement beginning within a few days. Complete recovery, however, is usually delayed, requiring from one to three months. In the occasional case, as the convulsions disappear, residual complications become apparent in the form of paresis of the various limbs (Comby[12] and Stephan[11]). Results of examination of the spinal fluid have been reported in only a few of these cases and in all have been normal.

In the three types of cerebral complication just described, the symptoms appear at the height of the pneumonia and have, therefore, been suspected of resulting from a toxic condition due to the high temperature. Although this suspicion may be warranted in some cases, the occurrence of similar neuropsychiatric syndromes during convalescence and after the temperature has been normal for days, the delayed recovery, the occasional increased cell count of the spinal fluid and the permanent residuals certainly suggest some additional causative factors besides the pyrexia.

4. *Lethargic Type* (cases 2 and 4).—This is by far the most unpredictable form of complication and occurs with equal frequency during the height of the illness and during convalescence, when the patient seems to be recovering. The onset is always dramatic and abrupt, with the patient suddenly becoming unresponsive and stuporous within a period of minutes or hours. This lethargic or stuporous state lasts for hours, days or even weeks and then almost invariably begins to recede slowly, requiring many weeks for complete recovery. As the lethargy disappears and the patient becomes more responsive, scattered associated disturbances become apparent. Many patients reveal motor aphasia or scattered motor weaknesses that persist for weeks or months. Recovery, although delayed, is the rule. The spinal fluid is usually normal, even though in 1 case of Garzón[14] there were 120 cells, of which 84 per cent were mononuclear leukocytes.

5. *Hemiplegic Form* (case 6).—This form of complication no doubt comprises the most spectacular of the symptoms and emphasizes the importance of caution in evaluating the prognosis even after mild pneumonia. The onset

is usually sudden and occurs from a few days to a few weeks after the patient's temperature has returned to normal and during a period when recovery would seem inevitable. The severity of the pneumonic process plays no part in the incidence of this complication, since it may be seen in patients in whom the original pneumonia was mild. The motor involvement may be complete or partial or may involve one or more limbs. It usually consists of a severe hemiparesis. There is no predilection for any particular side of the body. In a few cases the motor weakness is not noticed until the patient attempts to walk after a prolonged period of rest in bed. The cell count of the spinal fluid is usually normal, although a pleocytosis has been reported (Grenet and associates [24]). Recovery is delayed and begins in about two weeks. Improvement is slow, requiring months or years for complete recovery. In about half the cases, residual weakness can be expected. Buchanan [18] reported 1 case in which recurrent weaknesses occurred over a period of four years, with resultant right hemiplegia and ataxia.

COMMENT

Probably one of the most puzzling problems concerning the involvement of the central nervous system in pneumonia is that regarding the actual nature and cause of such complications. In attempting to arrive at any etiologic interpretation, one must keep in mind certain definite clinical facts, all of which tend to point to a common factor in most cases. Pneumonia, as is well known, can be caused by numerous different organisms, such as Streptococcus (Miller and Lusk [25] and Small [26]), Staphylococcus (Chickering and Park,[27] Reimann [28] and Baker [29]), Pneumococcus, influenza bacillus (Goodpasture and Burnett [30] and Hall, Stone and Simpson [31]) and viruses (Kneeland and Smetena [32] and Reimann [4]). In each type of pneumonia cerebral complications of a similar clinical and pathologic nature may occur. This variation immediately speaks against the etiologic organism of the pneumonia as the probable agent causing the encephalitis. It would be almost impossible for such a wide variety of different organisms to invade the brain through a similar hematogenous route and produce similar pathologic lesions. These facts narrow the etiologic field down to three remaining considerations:

1. *Toxic Theory.*—It is well known that scattered cerebral symptoms may occur as symptoms of toxemia secondary to pyrexia in any illness. This is particularly true in children, in whom vomiting, headaches, apathy and convulsions are extremely frequent. However, the occurrence of such symptoms following a mild pneumonic process and often after the pneumonia has subsided forces one to speculate on the presence of some other toxin, one not necessarily associated with the pyrexia but more directly related to the pneumonia and to the individual susceptibility to cerebral involvement.

2. *Virus Theory.*—A second theory would involve the activation by the pneumonia of some unknown virus which already was present in the brain. At present there is no proof for or against such a theory. Certainly the consistency of the clinicopathologic picture in spite of the wide variety of pathologic organisms involved in the pneumonia would tend to favor such a theory.

3. *Allergic Theory.*—Recently Ferraro [33] advocated an allergic reaction of the brain as the cause of the cerebral symptoms in postscarlatinal encephalitis. He assumed that an allergic phenomenon took place in the central nervous system during the infectious disease. Certainly in favor of this theory is the similarity of the pathologic lesions in our cases with those described by Ferraro as occurring in acute allergic reactions. The acceptability of this theory will be discussed in more detail in a later publication.

Finally, it seems imperative to emphasize again the significance of these changes in the

24. Grenet, H.; Isaac-Georges, P., and Desmarquest, J.: Deux cas d'encéphalite pneumonique, Bull. Soc. de pédiat. de Paris **33**:639, 1935.

25. Miller, J. L., and Lusk, F. B.: Epidemic of Streptococcus Pneumonia and Empyema at Camp Dodge, Iowa, J. A. M. A. **71**:702 (Aug. 3) 1918.

26. Small, A. A.: Pneumonia at a Base Hospital: Observations in One Thousand and One Hundred Cases at Camp Pike, Ark., J. A. M. A. **71**:700 (Aug. 31) 1918.

27. Chickering, H. T., and Park, J. H., Jr.: Staphylococcus Aureus Pneumonia, J. A. M. A. **72**:617 (March 1) 1919.

28. Reimann, H. A.: Primary Staphylococcic Pneumonia, J. A. M. A. **101**:514 (Aug. 12) 1933.

29. Baker, R. D.: Staphylococcal Pneumonia During Epidemic Influenza in North Carolina (1941), South. M. J. **35**:240, 1942.

30. Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**:177, 1919.

31. Hall, J. N.; Stone, M. C., and Simpson, J. C.: The Epidemic of Pneumonia Following Influenza at Camp Logan, Texas, J. A. M. A. **71**:1986 (Dec. 14) 1918.

32. Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Origin, Bull. Johns Hopkins Hosp. **67**:229, 1940.

33. Ferraro, A.: Allergic Brain Changes in Postscarlatinal Encephalitis, J. Neuropath. & Exper. Neurol. **3**:239, 1944.

central nervous system. In many cases, as exemplified by our cases 1 and 3, cerebral complications of a most severe degree followed relatively mild pneumonia. Such cases emphasize the importance of a careful neuropsychiatric examination of every patient ill with pneumonia to determine the presence of such cerebral symptoms. Any indication of involvement of the central nervous system should be an absolute indication for more prolonged care, with extreme caution in any prognostic evaluation offered. The favorable course of the pneumonia does not necessarily mean that recovery will be complete and uncomplicated. This study also suggests that many instances of mild cerebral involvement after pneumonia are probably being overlooked regularly. Such cases may be the etiologic basis of so-called unknown neuropsychiatric sequelae that are observed from time to time in children.

SUMMARY

Pneumonia, regardless of the causative organism, may be complicated by an involvement of the central nervous system.

The severity and frequency of the resulting encephalitis do not correlate with the severity of the pulmonary involvement. Relativly mild pneumonia may be followed by severe cerebral damage.

The clinical pictures produced by the involvement of the central nervous system can be divided into five groups, each showing certain definite clinical characteristics which may be of both diagnostic and prognostic significance. These groups are as follows: (1) that characterized by generalized symptoms of a nonspecific nature (headache, vomiting, lethargy and irritability); (2) delirious type; (3) convulsive type; (4) lethargic type, and (5) hemiplegic type.

PUTRID PULMONARY ABSCESS WITHOUT FOUL SPUTUM

(SHUT-OFF PULMONARY ABSCESS)

DANIEL STATS, M.D., AND HAROLD NEUHOF, M.D.
NEW YORK

During the past sixteen years, the pathogenesis, clinical manifestations, prognosis, complications and therapy of putrid pulmonary abscess have been discussed in detail by the group concerned with thoracic diseases at Mount Sinai Hospital. The clinical picture of acute putrid pulmonary abscess developed by these studies and publications differed in a number of respects from the accepted one. This difference was particularly striking regarding therapy, for it was learned that relatively early surgical unroofing of the abscess effected a rapid cure, prevented the appearance of complications and forestalled the development of bronchial distortions and fibrotic pulmonary changes. The validity of this departure from the previously accepted therapy has been amply proved by the results. Operative drainage of acute putrid pulmonary abscess is becoming accepted as the correct therapeutic approach.

An experience with several hundred cases of acute putrid pulmonary abscess not only has provided an understanding of the more typical or classic cases but also has revealed numerous variations. In most instances the diagnosis of acute pulmonary abscess is made easily. About one week after extraction of a tooth or tonsillectomy or often without any preceding unusual event, localized thoracic pain, cough and hemoptysis develop. The expectoration of foul sputum completes the picture. Roentgenologic examination of the chest reveals a circumscribed area of density or a pulmonary excavation up to several inches in diameter. A fluid level is often present. There are many variations of the clinical picture in relation to time of onset, character of cough or amount of sputum. In general, however, these variations do not make for difficulties in diagnosis. There are atypical roentgenologic features which may lead to errors in interpretation concerning the progress of the disease but not concerning the diagnosis in the presence of foul sputum.

There is, however, a not inconsiderable group of cases in which the foulness of the sputum either is absent or appears late, and these cases offer difficulties in diagnosis. Even with a great awareness of the disease on the part of the diagnostician, there were instances in which the diagnosis was long delayed or was not made. In recent years persistence in certain efforts, to which reference will be made, usually has provided the diagnosis. However, we may refer at once to a recent case of putrid pulmonary abscess in which the diagnosis was not made during several weeks of observation in the hospital despite such efforts, although it was strongly suspected throughout the period of observation. Prolonged delay in diagnosis may lead not only to increased morbidity and complications but also to death from spread of the disease beyond the limits of operative relief. Thus the necessity of establishing the diagnosis is of clinical importance and warrants full discussion.

The cases to be considered in this paper are instances of acute putrid pulmonary abscess without foul sputum. We have termed this variety "shut-off abscess" on the assumption that the bronchus communicating with the abscess is occluded as a result of an inflammatory reaction and cannot drain the contents of the abscess. In some instances a shut-off pulmonary abscess may go on to a putrid empyema, creating a special problem in diagnosis and therapy. The subject of putrid empyema without foul sputum (which we have termed "surprise" putrid empyema) will be discussed elsewhere.

The sole distinctive feature of a putrid pulmonary abscess is the foul or fetid odor. There are other clinical features which will often offer diagnostic leads, but it is on the odor of the sputum that the most reliance must be placed. When this odor is absent, the likelihood is great, but not absolute, as we shall show, that the pulmonary lesion is not of this nature. Therapy is based largely on the presence or absence of foul sputum. However, foul and gangrenous acute or subacute pulmonary abscesses may exist for months or longer in exceptional instances without foul sputum or foul breath.

The foulness of the sputum in connection with pulmonary abscess obviously depends on the

From the medical services and the surgical service of Dr. Harold Neuhof, Mount Sinai Hospital.

patency between the seat of the disease and the draining bronchi. An odor will not be present if bronchial edema and secretion effectively seal the bronchial lumen from the abscess proper. There is no reason to believe that the abscess differs in any other respect from the typical putrid abscess. It can be said with reasonable assurance that most, if not all, putrid pulmonary abscesses are shut off to some extent. Thus a characteristic feature is the bronchoscopic finding of edema of the bronchus leading to the abscess. Another feature to be noted in many cases is that the sputum, after being at first foul and expectorated in large quantities, is thereafter only intermittently foul; in other cases there is no history of foul sputum after the initial episode. The difficulty in visualizing the cavity by the introduction of radiopaque fluid is well known. Although the diagnosis is much more readily made when the abscess is only partially shut off, there is no discernible difference in the pathologic characteristics of the two varieties. In both, the abscess is usually of substantial proportions, situated superficially within the lung with overlying visceroparietal adhesions. However, in the truly shut-off abscess a far greater tendency toward invasion of the pleura can be anticipated; the possibility always exists of late perforation of the shut-off abscess into the bronchial tree. The question of the existence of smaller abscesses ("cortical") from which foul sputum is never derived and which are presumed to be sources of putrid empyema is a separate one which will be discussed elsewhere under the title "Putrid Empyema Without Foul Sputum."

The discussions of a decade ago concerning the pathogenesis of the various types of pulmonary abscess have ceased for the most part in recent years. Almost all observers now believe that putrid pulmonary abscess is due to aspiration of infected material, which is assumed to lodge in a sublobar bronchus, producing a severe acute necrotizing inflammation, edema and at least partial occlusion of the lumen. The bacteria contained within the bronchus multiply and spread to the neighboring blood vessels and lymphatics, causing vascular thrombosis. At the same time, they infiltrate the segment of lung (bronchopulmonary segment) supplied by the more or less occluded bronchus, producing necrosis and a gangrenous inflammatory process. From the beginning a putrid pulmonary abscess includes a bronchial lesion, and fair-sized bronchi are involved. The appearance of foul sputum, usually within two weeks of the inception of the lesion, is evidence that the abscess which has formed either has drained through the communicating bronchus, the edema of which has subsided, or has perforated into the bronchus. In no more than 5 per cent of our cases was such drainage lacking, but this percentage represents the group in which the diagnosis of putrid pulmonary abscess was difficult. There is no obvious explanation for the shut-off type. At operation the appearance of the abscess cavity with its communicating bronchial orifices is identical with that of other abscesses. One can only assume that the persistence of occlusion of the communicating bronchus is caused by edema and lodgment of detritus.

The observation of putrid pulmonary abscess without foul sputum is not new, although this series appears to be the first of such cases to be gathered and studied. Lord [1] in 1919 mentioned that "in very rare instances the sputum and the breath are not malodorous and the absence of the bad odor is, therefore, not an assurance against abscess. . . ." Wessler and Jaches [2] noted the rupture of "cortical pulmonary abscesses into the pleural cavity as a cause of putrid empyema. Eggers [3] suggested the presence of similar occurrences in his case reports (cases 2, 3 and 5). Neuhof and Wessler [4] in 1932 offered the first distinctive description of such cases, stating that "the expectoration of foul pus does not occur in the small cortical type of lung abscess and in exceptional cases of shut-off abscesses." The point was reiterated by Neuhof and Hirshfeld [5] and Touroff and Moolten [6] several years later.

The cause of shut-off pulmonary abscesses apparently is the same as that of other acute putrid abscesses. In a study [7] dealing with the etiology and the pathogenesis of acute putrid pulmonary abscess, it was pointed out that an obvious cause was not present in 64 per cent of 115 cases. In these, a large percentage of the patients had significant gingivodental infections. It was hypothesized that abscesses of obvious cause resulted from aspiration of infective matter

1. Lord, F. T.: Pulmonary Abscess, in Contributions to Medical and Biological Research, Dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919, vol. 1, pp. 640-649.

2. Wessler, H., and Jaches, L.: Clinical Roentgenology of Diseases of the Chest, Troy, N. Y., The Southworth Company, 1923.

3. Eggers, C.: Lung Abscess Complicated and Hidden by Empyema, Arch. Surg. **12**:338 (Jan., pt. 2) 1926.

4. Neuhof, H., and Wessler, H.: J. Thoracic Surg. **1**:637, 1932.

5. Neuhof, H., and Hirshfeld, S.: Ann. Surg. **100**: 1105, 1934.

6. Touroff, A. S. W., and Moolten, S. E.: J. Thoracic Surg. **4**:559, 1935.

7. Stern, L.: J. Thoracic Surg. **6**:202, 1937.

into small bronchi. The usual etiologic factors were general anesthesia, extraction of a tooth, coma and tonsillectomy or other operative procedures within the mouth, nose or pharynx. In cases without such factors, it was felt that anaerobically infected material from the gums and teeth had been aspirated during sleep or possibly at other times. In the series of shut-off abscesses presented here, the etiologic factors were similar. One patient had a tooth extracted three weeks before the onset of the disease, and another underwent a thyroidectomy under general anesthesia. In the remaining cases, there was no obvious cause, but most of the patients had grossly diseased teeth or gums or excess tartar.

The clinical picture of the shut-off type of pulmonary abscess depends on the size of the pulmonary lesion, its position, the imminence of or the actual existence of perforation into the pleural space, the extent of the pleural infection and the presence of unrelated pulmonary or other disease. If the pulmonary lesion is of substantial size, the main symptoms are likely to be cough and expectoration. These vary, however. In 1 case, there was as much as 14 ounces (420 cc.) of nonfoul sputum daily, while in another the sputum was scant. In some instances, a gangrenous pulmonary abscess is so well tolerated locally, and occasionally systemically, that the symptoms are insignificant. Cough may be slight or in rare instances completely lacking. It may be of a persisting hacking nature, accompanied with sputum at times, and may be productive of blood. Not only its severity but also its frequency may vary greatly. The cough may disappear for intervals and then recur. Bizarre courses have been observed. The relative mildness of cough and expectoration in the presence of a substantial pulmonary lesion may be a striking feature of the shut-off abscess.

Either the presence or the absence of a pronounced constitutional response, such as a high level of leukocytes and fever, may be disproportionate to the size of the abscess. The clinical picture often is alarming when the lesion has spread to the pleura with extensive putrid pleural infection. To this there may be added respiratory embarrassment if there is displacement of or pressure on mediastinal structures.

Pain is a general guide to the position of the lesion. Most putrid pulmonary abscesses are accompanied in some stage of their development (usually at the onset) with pains in the chest, often severe. The area of pain usually points to the site of pleuritis. When in rare cases the lesion faces an interlobar fissure, the diaphragm or the mediastinum, the location of the pain may be at variance with the situation of the abscess or pain may be absent. The importance of the appreciation of the significance of pains in the chest is greater in putrid pulmonary abscess than in many other forms of pulmonary disease. Pains in the chest almost always mean pleural involvement. In all cases, with rare exceptions, productive pleuritis seals the visceral and parietal pleurae over the lesion. The acute inflammatory element usually subsides in a short time, and with its subsidence the pain often disappears. Recurrence or persistence of severe pain indicates further pleural involvement; it strongly suggests an extension of the gangrenous pulmonary lesion toward the pleural surface and possibly an imminent empyema.

The factors responsible for spread to the pleura are not entirely known. In certain otherwise typical cases of uncomplicated putrid pulmonary abscess, sudden or gradual extension of the lesion to the pleura may occur without discernible cause. It is logical to assume that one important factor favoring spread to the pleura is absence of drainage of the abscess through the bronchial tree. Although our cases are too few for statistical analysis, they suffice to show that extension to the pleura is more common in shut-off abscesses than in abscesses with foul sputum. Pain in the chest was a more frequent and persistent symptom in these than in draining pulmonary abscesses. There were cases in which an unusually virulent infection appeared to exist. In these, severe pain in the chest at the onset and its persistence for days even in the complete absence of cough were evidence of almost immediate spread to the pleura, with the early formation of an empyema.

It was necessary to revert to the question of pain in acute putrid pulmonary abscess, because its correct interpretation has, in our experience, been of value in solving an otherwise difficult diagnostic problem. The differentiation of this pain, when the other features of the case have been considered, from that of the pleuritis which accompanies pneumococcus or other forms of pneumonia has usually been possible. In shut-off acute putrid pulmonary abscess, pain often is apoplectiform in suddenness and severity and is incapacitating. Once established, it tends to persist for days or weeks. It may remain fairly severe or may vary considerably, but it usually continues.

Physical examination is not of decisive diagnostic assistance. However, in the presence of a pleural infection (empyema) there may be cyanosis, dyspnea and grunting respirations, and the trachea and mediastinal structures may be displaced. Examination of the chest may reveal

little or nothing abnormal; dulness, abnormal breath sounds and rales may be found. When considerable fluid is present in the parietal pleural cavity, the well known signs may be found. A splash may be audible on succussion or indeed may be described by the patient if fluid and air coexist. A symptom of some importance as evidence of a severe pleural infection is localized tenderness of the thoracic wall in the region of severe pain. This, however, occurs in nonputrid pleural infections as well. That clubbing of the digits is likely to occur early in the course of putrid pulmonary infection and at times to be of diagnostic importance is well known. The absence of clubbing has no weight in a decision for or against a putrid infection.

The densities and rarefactions seen on roentgenographic examination in cases of shut-off abscess may be difficult to interpret. They are of no aid in a differentiation between a putrid and a nonputrid infection. When the pulmonary lesion is small, its roentgenographic counterpart is relatively insignificant. In 1 case nothing more than a small area of pulmonary infiltration was observed. In another, in which a large abscess was subsequently demonstrated, an extensive subapical density with the characteristics of a tuberculous or neoplastic infiltration was seen. A fluid level in an abscess cavity usually means a fairly free communication with a bronchus. In most cases of shut-off pulmonary abscess the complicating pleural involvement obscures or modifies the pulmonary shadow to such a degree that it becomes unrecognizable in films. The familiar shadows of a localized or total pleural effusion or hydropneumothorax may be seen. The presence of multiple fluid levels usually means a loculated pyopneumothorax. A roentgenologic picture which often is difficult to interpret is seen in cases of infrapulmonary or interlobar pyopneumothorax. In such instances the general impression is that of a large pulmonary abscess with a fluid level. In all cases of suspected putrid pulmonary infection, lateral and oblique views of the thorax and occasionally sectional roentgenograms are necessary for correct interpretation and accurate localization of the lesion.

The preceding discussion of the features of shut-off putrid pulmonary abscess must create the impression that the clinical picture is subject to great variation, and that is quite true. The diagnosis can be predicated only on an awareness that the lesion may exist. It is not too much to say that the features just discussed must be kept in mind in all cases of acute pulmonary infection in adults, conceding the fact that pneumonia or bronchopneumonia due to various organisms is much more common than shut-off putrid abscess. The occasional occurrence of shut-off pulmonary abscess, the tragedy that often results if the diagnosis is long delayed and the recovery that may be anticipated with reasonably prompt diagnosis and therapy warrant careful consideration of the existence of a lesion. Attention should be all the more focused on the possible existence of a shut-off abscess in cases with some of the features of abscess and with no response to chemotherapy.

The history of persistent pain in the chest, the physical finding of flatness on percussion and the roentgenographic demonstration of pleural fluid point to a complicating pleural infection of a shut-off pulmonary abscess. The extent and character of the empyema are variable. In most cases the empyema is extensive but not total. Air often accompanies the fluid. At operation the external surface of the parietal pleura may reveal acute inflammatory changes and edema. Entrance into the empyema usually is signalized by the escape of very foul thin fluid and air. At other times there may be a large quantity of serous nonodorous sterile fluid in the pleura, or such fluid may be loculated about a smaller collection of foul fluid. In impending perforations of the abscess into the pleural cavity, clear fluid with a faint foul odor may be observed. The sterile fluid is a "sympathetic" effusion. Its presence indicates severe pleural irritation. After evacuation of an empyema the partially collapsed lung covered by necrotic material may be seen. A shallow or moderately deep dirty excavation in the pulmonary parenchyma (the abscess) may be discernible, or a small opening may lead to a large underlying lesion.

The presence of a complicating pleural infection in cases of shut-off abscess suggests that by aspiration of the chest the character of the fluid can be ascertained and the diagnosis of a putrid infection established. The aspirating needle is a valuable but dangerous diagnostic instrument. To use the instrument intelligently one must take great care to locate the fluid accurately. Careful roentgenologic study must precede aspiration. In 4 of the cases characterized by empyema, aspiration provided the means for the detection of the putrid infection. In each of these, several aspirations had to be performed before the foul material was reached. Not infrequently only a "sympathetic" effusion is encountered. This should never leave one satisfied that the basic lesion has been discovered. The presence of such fluid always suggests the possibility (or probability) that an empyema may be found at an adjacent site. The danger of thoracentesis in the presence of a putrid pleural

infection is in infection of the thoracic wall. The occurrence of a putrid phlegmon of the wall may prove fatal. Whenever foul fluid has been disclosed by aspiration, immediate operation is imperative, and the tract of the needle is split open at the same time.

The diagnosis in our cases of shut-off abscess was based on the long interval between the onset of the disease and the appearance of foul sputum or of putrid empyema. In 5 of the 10 cases foul sputum was expectorated between five and sixteen weeks after the onset, and the diagnosis was thereby established. In 4, foul pleural fluid was aspirated. In 1 case, the diagnosis was determined only at autopsy. In another (not included in this compilation), observed in the hospital for many weeks, the abscess was still almost completely confined to the lung when aspiration unexpectedly revealed foul pus.

The treatment of acute putrid pulmonary abscess is often surgical. It is not necessary to present the detailed evidence for the view we hold, for this has been presented elsewhere.[8] The almost uniform satisfactory response to operation and the low operative risk must be balanced against the dangers inherent in a policy of watchful waiting. In any event, operation is imperative for shut-off abscess. In 2 of the 10 cases operations were not performed, in 1 because the expectoration of foul sputum on one occasion after four weeks of mild illness represented the evacuation and spontaneous subsidence of a small abscess and in the other because the diagnosis was not made. In all the others operation was performed as soon as the diagnosis of putrid pulmonary abscess with or without empyema was made.

In this series of 10 cases there were 2 deaths, 1 of which was avoidable.[9] The diagnosis was not made in case 3. The autopsy disclosed a small ruptured putrid abscess and a large putrid empyema. In case 5, which was encountered early in our experience, death occurred several weeks after drainage of a small empyema. In that instance, it was not possible to locate the main focus of disease. A ruptured pulmonary abscess and another putrid empyema were not found until postmortem examination. In this instance present day methods of locating intrathoracic lesions might have led to drainage of the unopened foci.

There can be anticipated a significant improvement in a patient's condition within a few days after the operation and a virtual complete subsidence of symptoms and signs referable to the abscess within about two weeks. In the absence of these favorable developments an undrained focus can be assumed to be present. The uniform and rapid clinical improvement of seriously ill patients with putrid pulmonary infections after adequate surgical drainage should provide the necessary stimulus to early diagnosis and treatment.

Shut-off lesions comprise about 5 per cent of all the acute putrid pulmonary abscesses which we have observed in the hospital. The subjoined table offers a summary of 10 well documented cases in our records. A number of additional cases of shut-off abscess were not included because of incomplete data. The following 2 cases have been selected as illustrative of the problems which arise in the diagnosis and the management of shut-off putrid pulmonary abscess.

CASE 1.—The patient was a 43 year old man whose illness started ten weeks before his admission to the hospital with cough, fever, chilly sensations and stabbing pain in the upper right side of the chest and behind the right shoulder. The pain recurred mildly from time to time. The cough and expectoration became more severe, and numerous small hemoptyses occurred. A foul odor was never observed. Fever and loss of weight finally brought the patient to the hospital.

Examination revealed a chronically ill man, with moderate gingivodental disease. Physical examination showed that the lungs were clear. The patient remained in the hospital for six weeks before a diagnosis was established. He had a low grade fever and continued to sweat and lose weight. The cough varied in severity but was generally rather severe. From 5 to 14 ounces (150 to 420 cc.) of nonodorous purulent sputum was expectorated daily. Repeated search for tubercle bacilli revealed no organisms. Occasional mild pain in the chest was experienced. Bronchoscopic examination was performed on four occasions. Purulent material without a foul odor was seen coming from the paravertebral branch of the bronchus of the upper lobe of the right lung. Numerous roentgen examinations revealed only an area of pneumonic infiltration in the posterior portion of the axillary part of the upper lobe of the right lung. The lesion did not change in size. Bronchography with iodized poppyseed oil was not helpful. One day, sixteen weeks after the onset, the patient expectorated several ounces of extremely foul sputum. Roentgenograms now revealed a large cavity, with a fluid level at the site of the previously observed infiltration.

Thoracotomy and pneumonotomy, performed after mobilizing the scapula, revealed a pulmonary cavity containing inspissated foul pus. The lining of the abscess was partly sloughing and partly smooth and glistening. Numerous bronchial openings were visible. After being completely unroofed, the cavity was packed.

The postoperative course was prolonged, and the abscess cavity closed slowly. At follow-up examination fifteen months later, the operative incision was found to be healed and the patient was asymptomatic.

This case is unique and is the only one in our series that demonstrates the development under

8. Neuhof, H., and Hurwitt, E.: Ann. Surg. **118**: 656, 1943.

9. Four recently observed operative cases, none of them fatal, can be added.

observation of a subacute or almost chronic putrid pulmonary abscess without foul sputum. The failure of this abscess to extend to the pleura to form an empyema also is exceptional. The fact that the diagnosis could not be established despite four bronchoscopic examinations is evidence of a completely shut-off putrid pulmonary abscess.

her readmission, the pain suddenly became extremely severe and the temperature rose to 105 F.

On her admission the patient was cyanotic and tachypneic. The mediastinal structures were shifted to the right, and there were signs of pleural fluid over the entire left side of the chest. The thoracic wall was tender. Clubbing of the digits was not present. Roentgen examination revealed a diffuse clouding of the entire left side of the chest.

Putrid Pulmonary Abscess Without Foul Sputum: An Outline of Ten Cases

Case	Onset	Pain	Cough	Expectoration	Hospital Stay Before Diagnosis, Days	Duration of Disease	Roentgenographic Appearance	Size of Pulmonary Abscess	Extent of Pleural Infection	Result
1	Cough, gradual	At onset for a few days; mild	Persistent and moderately severe	Profuse but nonfoul except just preceding operation	42	16 weeks	Pneumonic infiltration	Large	None	Recovery
2	Pain, sudden	Moderate for 20 weeks at onset	Persisted mildly after second week	1 to 3 oz. (3.7 to 11.1 cc.) daily; nonfoul except once 6 weeks after onset	14	6 weeks	Small pneumonic infiltration	Small	None	Recovery
3	Pain, sudden	Severe at onset; persisted mildly	Mild; beginning 3 days after onset	Not foul; 1 to 3 oz. daily	17	20 days	.....	Small	Moderate; parietal empyema	Death; patient not operated on
4	Infection of upper respiratory tract, gradual	1 week after onset; severe; persisted with remissions and exacerbations	Mild from onset; persistent	Scant, nonfoul	Diagnosis on admission	5 weeks	Pneumonic infiltration and pleural effusion	Small	Total; parietal empyema	Recovery
5	Infection of upper respiratory tract and pain, gradual	Gradually increasing severity; persistent	Mild	Scant, nonfoul	10	24 days	Pleural effusion; later fluid levels appeared	Moderate	Moderate; interlobar and infrapulmonary empyema	Death; undrained pulmonary abscess and empyema
6	Cough, gradual	Severe; 2 weeks after onset; persistent with exacerbations and remissions	Mild for 2 weeks and then stopped	Scant; questionably foul on 1 occasion 2 weeks after onset	Diagnosis on admission	4 weeks	Pneumonic infiltration and small pleural effusion	Moderate	Moderate; parietal empyema	Recovery
7	Cough, gradual	Severe for 2 weeks after onset	Moderate from onset	Several ounces daily; foul immediately before operation	1	15 days	Pleural effusion	Large	Moderate; parietal empyema	Recovery
8	Cough and fever, gradual	Began 2 weeks after onset; mild for 3 weeks, then severe	Mild but persistent	Scant, not foul	14	8 weeks	Loculated pyopneumothorax	Small	Moderate; infrapulmonary empyema	Recovery
9	Cough and fever, gradual	Started 2 weeks after onset; severe; recurred from time to time for 6 weeks	Mild but persistent	Scant; not foul until 8 weeks after onset	42	8 weeks	Effusion; later loculated pyopneumothorax	Moderate	Moderate; interlobar empyema	Recovery
10	Pain, sudden	Severe; remissions for 5 weeks	Slight; 4½ weeks after onset	Scant, not foul	Diagnosis on admission	5 days	At first pneumonic infiltration; later fluid level	Very large	None	Recovery

Case 2.—Six weeks before her admission to the hospital, this 60 year old woman had a thyroidectomy under general anesthesia. The postoperative course was complicated by a ten day febrile episode characterized by slight cough without expectoration and by indefinite mild discomfort in the left side of the chest. Roentgen examination revealed an area of pneumonic infiltration in the lower lobe of the left lung. The temperature gradually subsided, and the patient was discharged from the hospital. Thereafter she experienced intermittent mild discomfort in the left part of the chest, occasional cough and low grade fever. Two days before

The patient was observed for the next two weeks, during which time she remained acutely ill. The pain diminished in severity but persisted, and the cough increased somewhat; but nothing more than scant nonodorous sputum was expectorated. Subsequent roentgenograms revealed the development of a large fluid level. The temperature varied between 102.5 and 100 F. Five thoracic taps were done, but only turbid, nonfoul, sterile pleural fluid was obtained. Sulfapyridine did not affect the clinical course. Finally, the sixth tap, two weeks after admission, disclosed foul pus, and immediate operation was performed.

A parietal "sympathetic" effusion was traversed before a large infrapulmonary pyopneumothorax was entered and drained. A small, perforated putrid pulmonary abscess was seen on the inferior surface of the lower lobe, and this was unroofed. All the recesses of the pulmonary cavity and the infected pleura were packed. The drained areas soon became clean. A bronchial fistula was present for several days. There was rapid symptomatic improvement. The patient was discharged in three weeks. Follow-up examination six weeks later revealed the patient to be in excellent condition and the wound completely healed. The patient was found to be well at a follow-up examination one year after her operation.

The history, the clinical and roentgenographic data, the operative findings and the postoperative course are characteristic of shut-off acute putrid pulmonary abscess with putrid empyema. The site of perforation in the infrapulmonary space led to a localized collection of pus situated away from the parietes. It was for this reason that only "sympathetic" fluid was so often withdrawn on exploratory puncture.

SUMMARY

The early appearance of fetid sputum establishes the diagnosis of acute putrid pulmonary abscess in the great preponderance of cases. Foul sputum does not appear at all or makes its appearance much later than usual in about 5 per cent of the cases. On the basis of the assumed mechanism, the term shut-off pulmonary abscess appears appropriate for such cases. The great tendency of shut-off abscesses to invade the pleura comprises a special feature. The clinical manifestations with and without pleural invasion and the difficulties in diagnosis in the absence of fetid sputum must be carefully considered. The diagnosis should be entertained when (1) a cause for a putrid pulmonary abscess exsists (or, in the absence of a cause, dental hygiene is poor); (2) thoracic pain is severe, prolonged or recurrent; (3) cough and expectoration are minimal or absent, and (4) the roentgenogram reveals persistent pulmonary infiltration with or without pleural effusion. There are grave dangers inherent in a too long delayed diagnosis, but there is a likelihood of a correct diagnosis if the possibility of this lesion is borne in mind. The excellent results which can be achieved by adequate operations on the pulmonary abscess as well as on the complicating empyema, which is often present, provide an additional incentive to establishing the diagnosis of shut-off putrid pulmonary abscess.

SULFONAMIDE COMPOUNDS AND PENICILLIN

THE EFFECT OF COMBINED THERAPY ON EXPERIMENTAL INFECTIONS IN MICE

ERNEST H. SULTAN, M.D.; DORIS W. JENKINS, A.B., AND WINDSOR C. CUTTING, M.D.
SAN FRANCISCO

Penicillin and one of the sulfonamide compounds are frequently used simultaneously in treatment of serious infections in an attempt to enhance the therapeutic effect. Ungar,[1] in 1943, reported that sulfapyridine potentiated the action of penicillin, both in vitro and in a limited number of infected mice. Soo-Hoo and Schnitzer[2] confirmed Ungar's claim that penicillin and various sulfonamide drugs were synergistic in combatting streptococcic infections in mice. They also showed that penicillin could prevent the inhibiting action of paraaminobenzoic acid on the sulfonamide drugs. This observation suggested that, although penicillin and the sulfonamide drugs are presumed to act by different mechanisms, the combined effect might be greater than a summation and might represent a potentiation due to the inhibition by penicillin of the action of paraaminobenzoic acid present in pus and exudates and even in normal tissue fluids. T'ung[3] studied the in vitro effects of sodium sulfathiazole and of penicillin, alone and in combination, on several strains of Brucella organisms. In about half the strains there was susceptibility to the drugs individually, and there was an enhanced bactericidal effect when the combination was used. In similar in vitro studies on Actinomyces bovis and related organisms, Dobson and Cutting[4] were unable to demonstrate any important increase in inhibition when sulfonamide compounds and penicillin were used simultaneously.

Because of the therapeutic implications in the suggestion of additive or synergistic effects through the use of the two chemotherapeutic agents together, the problem was studied in bacterial infections in mice.

REPORT OF EXPERIMENTS

Pneumococcic Infection.—White mice weighing about 20 Gm. each were given intraperitoneal injections of 0.5 cc. of a 1:100 dilution of a twenty-four hour culture in blood broth of pneumococcus type I recently isolated from a patient. One or two days later, depending on when the mice showed signs of severe illness, treatment was started. In series 200 and 201, 10 mg. of sodium sulfadiazine or 10 units of penicillin, or both, was injected subcutaneously twice daily for four days. In series 202, 203, 205 and 206, 5 mg. of sodium sulfadiazine or 20 units of penicillin, or both, was injected subcutaneously twice daily for four days. In each series, the control group and each test group consisted of 5 or 10 mice. The results, based on the number of mice surviving after one week, showed a slightly enhanced effect with the combined drugs (table 1). Larger doses of penicillin (50 to 100 units twice daily) saved all mice.

TABLE 1.—*Survival of Mice After Pneumococcic Infection when Treated with Sodium Sulfadiazine or Penicillin or with Both*

Series	No. of Animals in Each Group	Number of Animals Surviving 7 Days: Control	Sodium Sulfadiazine, Mg. Twice Daily	Penicillin, Units Twice Daily	Sodium Sulfadiazine Plus Penicillin
200	5	1	5 (10)	2 (10)	3
201	5	0	2 (10)	0 (10)	3
202	5	0	0 (5)	0 (20)	2
203	5	1	2 (5)	0 (20)	3
205	5	0	1 (5)	1 (20)	2
206	10	0	4 (5)	2 (20)	5
Percentage surviving		6	40	14	50

Streptococcic Infection.—White mice weighing about 20 Gm. each were given intraperitoneal injections of 0.5 cc. of a 1:100 dilution of a twenty-four hour culture of G 27 K hemolytic streptococci. About six hours later treatment was started. In series 210, a dose of 5 mg. of sodium sulfadiazine or 20 units of penicillin, or both, was injected subcutaneously, twice daily for two or three days. In series 211, 212, 213 and 214, the dose of sodium sulfadiazine was 0.5 mg. and the

From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine.

1. Ungar, J.: Synergistic Effect of Para-Aminobenzoic Acid and Sulfapyridine on Penicillin, Nature, London **152**:245 (Aug. 28) 1943.

2. Soo-Hoo, G., and Schnitzer, R. J.: The Activity of Penicillin Combined with Other Anti-Streptococcal Agents Towards β-Hemolytic Streptococci in Vivo, Arch. Biochem. **5**:99 (Sept.) 1944.

3. T'ung, T.: In Vitro Action of Penicillin Alone and in Combination with Sulfathiazole, on Brucella Organisms, Proc. Soc. Exper. Biol. & Med. **56**:8 (May) 1944.

4. Dobson, L. G., and Cutting, W. C.: Penicillin and Sulfonamides in the Therapy of Actinomycoses: Report of Sixteen Additional Cases and in Vitro Tests of the Susceptibility of Actinomyces to Penicillin and Sulfadiazine, to be published.

penicillin was increased to 30, 40, 50 and 60 units twice daily respectively. In each series, the control group and each test group consisted of 5 or 10 mice. The results, based on the number of mice surviving after one week, showed that the combination of penicillin and sodium sulfadiazine was slightly superior to the individual drug (table 2). In the higher doses penicillin alone saved all the animals.

TABLE 2.—*Survival of Mice After Streptococcic Infection when Treated with Sodium Sulfadiazine or Penicillin or with Both*

Series	No. of Animals in Each Group	Number of Animals Surviving 7 Days: Control	Sodium Sulfadiazine, Mg. Twice Daily	Penicillin, Units Twice Daily	Sodium Sulfadiazine Plus Penicillin
210	5	1	4 (5)	0 (20)	4
211	5	0	2 (0.5)	0 (30)	3
212	5	0	1 (0.5)	0 (40)	2
213	10	1	8 (0.5)	7 (50)	10
214	5	1	2 (0.5)	2 (60)	4
Percentage surviving	10		56.6	30	76.6

COMMENT

The frequent clinical policy of using sulfonamide drugs and penicillin simultaneously is given a measure of support by the experimental results obtained. With both pneumococcic and streptococcic infections in mice, combined therapy in the doses used resulted in slightly better percentages of survival than therapy with either drug alone. While larger doses of either single drug might have given equally good or even better results, the experimental results still have clinical significance.

The doses of sodium sulfadiazine used, 1 to 10 mg. daily for a 20 Gm. mouse, are proportional on a weight basis to a daily dose of 3.5 to 35 Gm. for a 70 Kg. man. Although sulfonamide drugs are better tolerated by small animals than by human beings, the higher doses approach the margin of safety, and the combinations would obviously be superior to an increased dose of the sulfonamide drug. The doses of penicillin, 20 to 200 units daily, are similarly proportional to 70,000 to 700,000 units daily for an adult man. With the larger doses, all the animals were saved, and therefore no enhancement of action by the combination could be demonstrated. Nevertheless, even though these large doses are nontoxic, for infections with organisms more resistant to penicillin, for mixed bacterial infections or for grave illnesses, the most effective action of penicillin may not be obtained with them and combined therapy may be valuable. However, for highly susceptible infections, the combination would appear to offer no advantages and to possess the disadvantage of possible toxic effect from the sulfonamide drug.

The total effect of the combination of penicillin and a sulfonamide drug is far short of the sum of the individual effects, and potentiation, therefore, in the sense of an effect greater than an additive effect, is absent.

CONCLUSIONS

Pneumococcic and streptococcic infections in mice responded slightly more favorably to simultaneous treatment with penicillin and sulfadiazine than to treatment with either drug alone.

When doses comparable to those tried are used clinically, some enhancement of therapy may be expected from the combination.

Even when higher doses of penicillin are used, the desperate state of the patient or the resistance of the particular causative organism or organisms may warrant combined therapy.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

TULAREMIC MENINGITIS

REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH POSTMORTEM OBSERVATIONS

BYRON M. STUART, M.D., AND ROSCOE L. PULLEN, M.D.
NEW ORLEANS

Tularemia has been accepted generally as a systemic disease which frequently presents manifestations that may be interpreted as being septicemic in nature. It is logical, therefore, to suspect in case of a septicemic disease such as tularemia that almost every tissue of the body at some stage of the illness may be infected. Although evidence of meningeal irritation and involvement of the central nervous system are occasionally observed in cases of tularemia which terminate fatally, instances in which the existence of tularemic meningitis has been proved, either during life or by postmortem studies, are unusually rare, especially when one considers the frequency with which the lungs, liver, spleen and lymph nodes are involved in fatal cases of tularemia. Because invasion of the meninges by Bacterium tularense (Pasteurella tularensis) has been observed so infrequently, we have considered it worth while to report this case, which came to our attention in a recent review [1] of the cases of tularemia that have occurred at Charity Hospital since 1928.

As early as 1927, Francis and Callender [2] mentioned a case which was probably an example of tularemic meningitis. Again; in 1930, Francis [3] made mention of 5 fatal cases of tularemia terminating with severe meningeal symptoms. Haizlip and O'Neil [4] in 1931, however, were the first to demonstrate that the meningeal symptoms associated with tularemia were the result of invasion of the spinal canal by Bact. tularense. Subsequent cases have been reported by Bryant and Hirsch,[5] Hartman,[6] Pund and Hatcher [7] and David and Owens.[8] The last mentioned successfully isolated the infecting organism from the blood and spinal fluid of their 5 year old patient before death occurred. The table summarizes those cases considered acceptable as instances of tularemic meningitis.

REPORT OF CASE

S. J., a 34 year old Negro man, was admitted to the service for contagious diseases at Charity Hospital on Feb. 16, 1940. The patient had been perfectly well until five days prior to his admission, at which time he had a severe, shaking chill with profuse sweating. Several hours later, he began to have a severe headache, and his wife believed that he had a high fever at that time. The following day he felt well enough to return to work but continued to have a mild headache. No nausea, vomiting, diarrhea, cough, hemoptysis or other symptoms were present. He continued to feel "dumpy" until about thirteen hours before his admission to the hospital, at which time he rapidly became confused and disoriented and failed to recognize familiar people and objects. He apparently failed to hear what was said to him or at least failed to comprehend what was said. He would place his hands over his eyes occasionally and mumble incoherently. He was seen by a physician, who advised him to come into the hospital for treatment. The patient's past history and family history were noncontributory.

On admission to the hospital, he was observed to be a well developed, well nourished Negro man, 34 years of age, who was uncooperative, agitated, confused and disoriented and had to be restrained. His temperature was 100.4 F. by mouth, pulse rate 58 per minute and respiratory rate 20. The blood pressure was 130 systolic and 82 diastolic. The pupils reacted to light. There was no rigidity of the neck and no lymphadenopathy. Auscul-

From the Department of Medicine, Tulane University of Louisiana School of Medicine and Charity Hospital.

1. Pullen, R. L., and Stuart, B. M.: Tularemia: Analysis of Two Hundred and Twenty-Five Cases, J. A. M. A. **129**:495 (Oct. 13) 1945. Stuart, B. M., and Pullen, R. L.: Tularemic Pneumonia: Review of American Literature and Report of Fifteen Additional Cases, Am. J. M. Sc. **210**:223 (Aug.) 1945.

2. Francis, E., and Callender, G. R.: Tularemia: Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927.

3. Francis, E.: Tularemia, in Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1930.

4. Haizlip, J. O., and O'Neil, A. E.: A Case of Meningitis Due to Bacterium Tularense, J. A. M. A. **97**:704 (Sept. 5) 1931.

5. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis: Report of Case, Arch. Path. **12**:917 (Dec.) 1931.

6. Hartman, F. W.: Tularemic Encephalitis: Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, Am. J. Path. **8**:57 (Jan.) 1932.

7. Pund, E. R., and Hatcher, M. B.: Tularemic Meningitis: Report of Case with Postmortem Observations, Ann. Int. Med. **10**:1390 (March) 1937.

8. David, J. K., and Owens, J. N.: Tularemic Meningitis: Report of a Case and Summary of Previously Reported Cases, Am. J. Dis. Child. **67**:44 (Jan.) 1944.

tation and percussion revealed clear pulmonary fields. The heart rhythm was regular. There were no murmurs. Examination of the abdomen revealed no tender areas, masses or distention. The extremities were normal. The deep tendon reflexes were sluggish, and Kernig's and Brudzinski's signs were absent.

Laboratory studies at the time of the patient's admission revealed a hemoglobin content of 14.4 Gm. per hundred cubic centimeters and a white cell count of 11,200, with 81 per cent polymorphonuclear leukocytes, 16 per cent lymphocytes and 3 per cent monocytes. Examination of the urine revealed no abnormalities. The serologic reaction of the blood was negative for syphilis by both the Kline and the Kolmer test. Lumbar puncture on the day of his admission yielded spinal fluid under a pressure of 34 cm. of water, of turbid appearance and containing 960 white cells, with 60 per cent large lymphocytes and 40 per cent small lymphocytes. There was a 4 plus reaction for globulin. The value for sugar was 45.4 mg. per hundred cubic centimeters and for chlorides 643 mg. per hundred cubic centimeters, and the colloidal gold curve was 00012340220. A smear of the spinal fluid showed no organisms. Culture of the fluid showed no growth in twenty hours.

Several hours after his admission, the patient was still restless and agitated and was given paraldehyde. Lumbar puncture was repeated on February 17, with results similar to those of the previous day. On February 18 the patient began spitting up frothy, bright red blood. The respiration and pulse were poor; some degree of rigidity of the neck was noted, and examination of the chest still revealed nothing abnormal. The patient became comatose, and fluids were administered intravenously. On February 19 he had two generalized convulsions in thirty minutes. Breathing was stertorous. Seven and one-half grains (0.5 Gm.) of sodium amytal was given. An infusion of 3,000 cc. of 10 per cent dextrose in isotonic solution of sodium chloride was given. The white blood cell count was 14,100. On February 20 the patient's condition became much worse. Administration of oxygen by nasal catheter was begun on February 21. The white blood cell count was 9,400. The urine was normal. A spinal tap revealed that the cerebrospinal fluid was still turbid; 400 cells were present, and pressure was 24 cm. of water. Rales were heard bilaterally. A roentgenogram of the chest was interpreted by the roentgenologist as "showing increased density in the left lung from the level of the third to the level of the sixth rib anteriorly and slightly increased density of the right side in the perihilar zone. The picture was not characteristic of tuberculosis and was suggestive of pneumonia of the left lung." Full doses of sulfapyridine were prescribed and were given by the intravenous route. Infusions were continued. On February 22, the eleventh day of illness, the patient died.

Postmortem examination was performed by Dr. Emil Palik, of the department of pathology of the Charity Hospital, approximately five hours after death occurred. Following is the autopsy protocol.

Gross Pathologic Changes.—Body: The body was that of a well developed, well nourished Negro man, 34 years of age, measuring 175 cm. in length and weighing 152 pounds (69 Kg.). Rigor mortis was present and also body heat. The pupils were round and equal and measured 3 mm. each. The scleras were clear. The abdomen was flat. No edema was present. Oral hygiene was poor. The extremities and external genitalia revealed nothing unusual.

Peritoneal Cavity: The membranes of the peritoneal cavity were smooth and glistening. There were no adhesions or free fluid. The appendix, omentum and mesenteric lymph nodes appeared normal. The diaphragm extended to the fifth rib on the right and the sixth interspace on the left.

Pleural Cavities: The membranes of the pleural cavities were smooth and glistening. No free fluid or adhesions were present, and the lungs completely filled the cavities.

Pericardial Cavity: The pericardial surfaces were smooth and glistening. The pericardial sac was normal in size, shape and position. There was no free fluid or adhesions.

Heart: The heart weighed 350 Gm. The valves, endocardium and coronary arteries presented no significant abnormalities. The myocardium was pale red and firm.

Aorta: The aorta presented numerous small, pale yellow, atheromatous plaques.

Lungs: The right lung weighed 1,100 Gm.; the left weighed 850 Gm. The surfaces were smooth and dark red. On section, all lobes in both lungs presented confluent large and small dark red areas of consolidation. Some of these areas appeared moist; others, dry and granular. The hilar lymph nodes were edematous. The bronchial tree contained mucoid exudate. The vessels appeared normal.

Spleen: The spleen weighed 190 Gm.; it was dark red and moderately firm. On section, the malpighian corpuscles appeared prominent. No abnormalities were seen throughout the pulp, and the pulp scraped with moderate difficulty.

Liver: The liver weighed 2,100 Gm. It was reddish brown and moderately firm. On section, the normal architecture was seen. The gallbladder appeared normal and contained dark brown bile. The biliary tract and portal vein were normal.

Pancreas: The pancreas weighed 70 Gm.; it was moderately firm and pale gray. On section, the normal architecture was seen.

Gastrointestinal Tract: The gastrointestinal tract was normal in its entirety.

Adrenal Glands: The adrenal glands weighed 10 Gm. each. They were tan colored and soft. On section, the normal line of demarcation between cortex and medulla was seen.

Kidneys: The right kidney weighed 190 Gm.; the left weighed 210 Gm. They were pale red and moderately firm. The capsules stripped with moderate difficulty, revealing finely granular renal surfaces. On section, the cortices were found to measure 8 mm. each and were clearly demarcated from the medullas. The cortical striations were normal. The calices, pelves and ureters appeared normal.

Urinary Bladder: The urinary bladder contained a small amount of clear straw-colored urine. The mucosa was pale gray and smooth. The ureteral and urethral orifices were patent.

Genital Organs: The prostate, testes, seminal vesicles and urethra were normal.

Brain: When the calvarium was removed, the meninges were found to be intact, and when they were opened the cerebrospinal fluid was found to be clear. The brain itself weighed 1,470 Gm. The subarachnoid vessels were greatly dilated. The hemispheres were symmetrically developed. Over both of these there were a few patches of grayish white exudate, especially over the frontal region. These were limited to the sulci. There was no exudate apparent grossly at the base of the brain. No softenings could be felt. On section, no abnormalities could be seen within the brain substance and ventricles.

Summary of Reported Cases of Tularemic Meningitis

Author	Patient: Sex	Patient: Race	Patient: Age	Source of Infection	Form of Disease *	Duration of Disease Before Meningitis Developed, Days	Duration of Meningitis Before Death, Days	Spinal Fluid	Blood Counts	Agglutinations and Cultures of the Blood	Diagnosis Established
Haizlip and O'Neil [4]...	M	W	45	Rabbits and squirrel	U. G.	5	5	Cloudy; 2,100 cells; 70% polymorphonuclears; stain and culture negative	3,300 white blood cells; 60% polymorphonuclears; lymphocytes 36%; monocytes 2%	Agglutination in dilution of 1:40; culture of blood negative	Spinal fluid injected into guinea pig with positive reaction for tularemia
Bryant and Hirsch [5]...	M	W	48	Rabbit	U. G.	10	5	Cloudy; 400 cells; 84% monocytes; 10% polymorphonuclears; smear and culture negative; 230 mm. water pressure; Pandy reaction positive; 75 mg. per 100 cc. albumin	.....	Agglutination in dilution of 1:40 on 14th day	Inoculation of guinea pigs (postmortem) from splenic tissue of patient reproduced disease; focal lesions in meninges
Hartman [6].....	M	W	Middle-aged	Rabbits	U. G.	4	25	Bloody fluid; 145 white blood cells; culture of fluid negative; sugar 42 mg. per 100 cc.	11,500 white blood cells; 84% polymorphonuclears; lymphocytes 2%; monocytes 14%	Agglutination in dilution of 1:640 on 15th day; 1:1,280 on 17th day; culture of blood negative	Rising agglutination titers; lesions at necropsy interpreted as tularemia
Pund and Hatcher [7]...	F	N	12	?	U. G.	7	3	114 cells; 18 mm. mercury pressure; negative for globulin; Wassermann reaction negative; 200 cells; 22 mm. mercury pressure; smear negative	8,700 white blood cells; 65% polymorphonuclears; lymphocytes 35%	Culture of blood negative	Necropsy showed appendix, thymus, brain and uterus involved; blood agglutination in dilution of 1:640 and 1:1,280
David and Owens [8]....	F	W	5	Cat that had fed on rabbit viscera	U. G.	9 ?	4	Cloudy; 2,000 cells; 99% lymphocytes; 18 mg. per 100 cc. sugar; 4+ Pandy reaction; culture positive for Bact. tularense	17,000 white blood cells; 80% polymorphonuclears; lymphocytes 15%; monocytes 5%	Culture of blood positive on 2d day; culture positive on 4th day; sputum positive; culture of pus from the thumb positive	Culture of blood, sputum, pus from the thumb and spinal fluid positive; postmortem examination confirmatory
Stuart and Pullen.....	M	N	34	?	T.	5	6	Cloudy; 960 cells; 60% large lymphocytes; 40% small lymphocytes; 4+ globulin reaction; 45.4 mg. per 100 cc. sugar; 643 mg. per 100 cc. chlorides; smear and culture negative; colloidal gold curve, 00012340220	11,200 white blood cells; 81% polymorphonuclears; lymphocytes 16%; monocytes 3%	Culture of blood negative; no agglutination	Postmortem inoculation of laboratory animals

* U. G. indicates ulceroglandular; T. indicates typhoidal.

Microscopic Examinations.—Heart: The myofibrils, connective tissue and vessels appeared normal.

Lungs: In some areas the alveoli and bronchioles appeared normal. In other areas, the alveoli were filled with polymorphonuclear leukocytes and a small amount of fibrin. In some areas, the alveolar septums had been destroyed. Numerous macrophages containing tiny brown granules of pigment were present. The bronchioles contained acute inflammatory exudate and debris. The vessels appeared normal.

Spleen: The capsule, trabeculae, malpighian corpuscles and vessels appeared normal. No foci of necrosis were present.

Liver: The hepatic cords, portal spaces, central veins and sinusoids appeared normal. The submucosa and muscularis of the gallbladder were infiltrated by a moderate number of lymphocytes and plasma cells.

Miscellaneous Observations: The cells of the cortex and medulla of the adrenal glands appeared normal, as did the mucosa and muscularis of the intestine.

The islets, acini, connective tissue and vessels in the pancreas, the glomeruli, tubules and arterioles of the kidneys, the prostate lobules and stroma and the epididymal lobules and stroma all appeared normal.

Brain: In the meninges of most sections of the brain there were a few small and large round mononuclear cells, inflammatory in character. There was an abundance of yellow pigmented granules, some of which were free and some inside the large mononuclear cells. This infiltration was most severe in the choroid plexus. Here also were seen numerous psammoma bodies. All sections of the cortex showed extreme congestion and severe degeneration of ganglion cells, the latter being greatly out of proportion to the degree of inflammation. This swelling and disappearance of ganglion cells was also noted in the basal ganglions and in the brain stem. The ependyma of the lateral ventricles showed plaque formation and subependymal gliosis. In the medulla there were several subependymal petechiae.

Postmortem Bacteriologic Observations.—Culture of the blood showed no growth. Culture of the lungs revealed streptococci. Guinea pigs inoculated with substance from the lungs and the brain became ill and were examined by autopsy on the fourth day. Each showed numerous miliary lesions in the spleen consistent with the diagnosis of tularemia.

COMMENT

There was no clue as to the mode of infection in this case; and, since no evidence of ulceration or regional lymphadenopathy was present, tularemia was not considered as a diagnostic possibility. Although an occasional report [9] of meningeal symptoms associated with the typhoidal type of tularemia has appeared, this is, to our knowledge, the first proved instance of tularemic meningitis in which ulceration or regional lymphadenopathy was lacking.

One can determine from the table that the average duration of illness in 6 cases of tularemia before evidences of meningeal involvement appeared was seven days. Whether this may be interpreted as additional evidence in favor of a second bacteremia or invasion of the blood stream by Bact. tularense five or six days before death in fatal cases, as postulated by Foshay,[10] we are unable to state.

In an attempt to explain the pathogenesis of the meningeal involvement in cases of tularemia, three possible routes of invasion have been suggested. David and Owens [8] have expressed the opinion that the infecting organism may have been introduced into the subarachnoid space at the time of the initial lumbar puncture in their case, since bacteremia was present when the patient entered the hospital. Pund and Hatcher,[7] in interpreting their case, considered the meningitis secondary to the breakdown of an area of focal necrosis in the substance of the brain. The other suggested explanation is that the infecting organism reached the meninges directly by way of the blood stream.[8] In a disease in which evidences of bacteremia occur with considerable frequency, involvement of the meninges is to be expected in a certain number of cases. Tularemia is to be considered, therefore, in the diagnosis of obscure forms of meningitis, and, in turn, evidences of meningeal involvement should be sought for in gravely ill patients with tularemia.

Thus far, no patients with tularemic meningitis have recovered. Therapy is of no avail, though one should utilize all available chemotherapeutic agents, including penicillin and the sulfonamide compounds, and Foshay's antiserum.

SUMMARY

A case of tularemic meningitis was observed and studied. Five previous cases were collected from the literature. To our knowledge, our case is the first in which tularemic meningitis occurred in the typhoidal form of the disease.

9. Tillisch, J. H.: Case of Typhoid Tularemia, Proc. Staff Meet., Mayo Clin. **16**:205 (March 26) 1941.

10. Foshay, L.: Tularemia: A Study of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in 600 Patients, Medicine **19**:1 (Feb.) 1940.

INTRAVENOUS INJECTION OF ACACIA

CLINICAL AND PHYSIOLOGIC EFFECTS ON PATIENTS WITH NEPHROTIC EDEMA

JOHN B. JOHNSON, M.D., AND LLOYD H. NEWMAN, M.D.
WASHINGTON, D. C.

The management of edema in patients with chronic glomerulonephritis complicated by the syndrome of hypoproteinemia and massive proteinuria continues to be unsatisfactory. The immediate cause of the edema is the reduced osmotic pressure resulting from the hypoproteinemia. No clinical methods are available at present by which one can stop the proteinuria or stimulate production of plasma protein so that the plasma protein concentration will rise sufficiently to eliminate the edema.

Administration of acacia in the treatment of nephrotic edema was first reported by Hartmann in 1933.[1] Since that time, many clinical reports have appeared, and much experimental work has been done on this subject. For the most part these reports have been unfavorable, with the result that acacia is not used extensively in the treatment of nephrotic edema. The opposition to the use of acacia is based on the following observations:

1. Cases have been reported in which there was no significant reduction of edema in spite of large doses of acacia.[2]

2. When acacia is administered, there is almost invariably further reduction in the plasma protein concentration.[3]

3. In some patients tenderness and enlargement of the liver follow repeated injections of large doses of acacia.[2]

4. In postmortem studies of patients[4] and in experimental studies on dogs,[5] large deposits of acacia have been recovered in the livers. This and the two preceding observations have led to the opinion that acacia causes serious hepatic damage and therefore should not be used in the treatment of nephrotic edema.

In spite of these observations, the use of acacia in the treatment of nephrotic edema has recently been revived by Goudsmit and Binger.[6] Their reports seemed sufficiently encouraging to justify further clinical study.

The data to be reported here indicate that acacia, when combined with mercurophylline injection, is an effective means of treating nephrotic edema, even when other recognized methods of treatment have failed. Further, some of the objections to acacia therapy are shown to be unjustified.

MATERIALS AND METHODS

The acacia[7] used in this study was dissolved in distilled water and injected intravenously by the Murphy drip method at a concentration of 15 to 20 per cent. Determinations of plasma volume were made by using congo red according to the method of Keith, Rowntree and Geraghty as modified by Harris.[8] Hematocrit studies were done by the method of Wintrobe.[9] The amounts of acacia in plasma and in urine were determined by the method of Butt, Power and Keys.[10] The acacia content of tissues was determined by the same method after extraction of the triturated tissues with hot distilled water. The prothrombin time was measured by

From the Departments of Medicine and Biochemistry, Howard University School of Medicine and Freedmen's Hospital.

1. Hartmann, A. F.; Senn, M. J. E.; Nelson, M. V., and Perley, A. M.: The Use of Acacia in the Treatment of Edema, J. A. M. A. **100**:251 (Jan. 28) 1933.

2. (*a*) Dick, M. W.; Warweg, E., and Andersch, M.: Acacia in the Treatment of Nephrosis, J. A. M. A. **105**: 654 (Aug. 31) 1935. (*b*) Faulkenstein, D. F., and Jackson, R. L.: Acacia Therapy in a Child with Nephrosis, J. Pediat. **16**:700, 1940.

3. (*a*) Yuile, C. L., and Knutti, R. E.: Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia, J. Exper. Med. **70**:605, 1939. Goudsmit, A., Jr.; Binger, M. W., and Power, M. H.: Acacia in the Treatment of the Nephrotic Syndrome, Arch. Int. Med. **68**: 701 (Oct.) 1941. Dick, Warweg and Andersch.[2a] Faulkenstein and Jackson.[2b]

4. (*a*) Andersch, M., and Gibson, R. B.: Studies on the Effect of Intravenous Injections of Colloids, J. Pharmacol. & Exper. Therap. **52**:390, 1934. (*b*) Dick, Warweg and Andersch.[2a] Faulkenstein and Jackson.[2b]

5. Yuile and Knutti.[3a] Andersch and Gibson.[4a]

6. Goudsmit, A., Jr., and Binger, M. W.: Treatment of Nephrotic Edema, J. A. M. A. **114**:2515 (June 29) 1940.

7. The acacia used in these experiments was supplied by Eli Lilly and Company.

8. Osgood, E. E.: Congo Red Test, in A Textbook of Laboratory Diagnosis, ed. 3, Philadelphia, The Blakiston Company, 1940, p. 413.

9. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942.

10. Butt, H. R.; Power, M. H., and Keys, A.: Concentration of Acacia in the Serum, Its Rate of Excretion and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, J. Lab. & Clin. Med. **24**:690, 1939.

the Quick method.[11] The total plasma protein was determined by the Kjeldahl method and by direct nesslerization. The plasma albumin was determined by the same method after treatment with 22.5 per cent sodium sulfate to remove the plasma globulins. The mercurophylline injection[12] was given in distilled water intravenously.

OBSERVATIONS

Nine patients with chronic glomerulonephritis, hypoproteinemia and proteinuria and 1 patient with hyperproteinemia were given acacia intravenously on several occasions. Observations were made in order to study the effect of injection of acacia on plasma protein concentration, changes in plasma volume, excretion of acacia, edema and proteinuria.

TABLE 1.—*Effect of Intravenous Injections of Acacia on Plasma Protein Concentration*

Case	Hours After Injection	Plasma Protein, Gm. per 100 Cc.	Plasma Acacia, Gm. per 100 Cc.	Acacia Injected, Gm.
1	0	4.68	0.0	60
	20	2.81	2.07	
2	0	2.61	0.0	120
	24	1.98	1.70	
	72	1.96	1.43	
	144	2.93	1.07	
3	0	4.34	0.0	90
	20	2.83	1.37	
	44	2.75	1.41	
4	0	5.03	0.0	90
	24	2.51	1.87	
	72	2.60	1.91	
5	0	3.77	0.3	60
	24	2.35	1.87	
6	0	4.80	0.40	60
	24	3.25	2.02	
7A	0	8.3	0.0	90
	12	7.0	1.37	
7B	0	6.90	1.20	90
	8	5.02	2.61	
	144	6.60	....	
8	0	4.5	0.0	120
	22	2.5	1.57	

Table 1 summarizes the effect of the acacia on the plasma protein concentration in 8 of the patients. In all patients studied an immediate reduction in the plasma protein concentration was observed. This reduction was demonstrable at any period between eight and twenty-four hours after the injection of acacia. After about seventy-two hours the plasma protein concentration showed a slow but progressive rise toward the initial level.

This type of reduction in plasma protein concentration has been previously reported and is cited as one of the major contraindications of acacia therapy for patients whose concentration is already below the critical level. Some authors have interpreted this as evidence of hepatic damage. Certain of our data indicate that most of this depression in plasma protein can be explained on the basis of an increase in plasma volume incident to the hydrophilic effect of the circulating acacia.

Simultaneous changes in the hematocrit reading and in the plasma protein concentration were measured. From these data we have calculated the predicted depression in plasma protein concentration as a result of the increased plasma volume. The correlation between the observed and the predicted depression in plasma protein is shown in table 2. This correlation is sufficiently close to indicate that the depression of the plasma protein concentration observed after injection of acacia can be satisfactorily explained on the basis of dilution, which is brought about by the influx of fluid from the edematous tissues into the circulation.

The actual plasma volume was measured with congo red in case 8, listed in table 1. The control plasma volume in this case was 2,530 cc. Twenty-four hours after the injection of 120 Gm. of acacia, this patient's plasma volume was 3,570 cc. This increase of 38 per cent compares favorably with the 36 per cent increase calculated by the changes in the hematocrit reading. Several days later the study was repeated on this patient. The control plasma volume was 3,081 cc. Twenty-four hours after the injection of 90 Gm. of acacia, his plasma volume was 3,742 cc. This represents an increase of 21 per cent, as compared with an increase of 19 per cent calculated by the changes in the hematocrit reading. The clearance of congo red was normal in this patient, 69 per cent of the dye remaining in the plasma at the end of

TABLE 2.—*Correlation Between Observed and Predicted Concentration of Plasma Protein*

Case	Hematocrit Reading, %		Blood Volume, % Increase *	Plasma Protein, Gm. per 100 Cc.		
	Control I	After Acacia II		Control	After Acacia Observed	After Acacia Calculated †
1	33.2	23.8	39.5	4.68	2.81	2.94
2	33.5	23.0	45.6	2.69	1.98	1.60
3	41.5	28.0	48.2	4.34	2.83	2.40
	30.0	37.5	9.0	2.80	2.20	2.48
4	42.5	27.0	57.4	5.03	2.51	2.51
5	42.0	32.5	27.7	3.77	2.35	2.56
6	30.0	26.0	15.4	4.80	3.25	3.94
7	45.0	38.5	19.5	8.3	7.0	6.14
8	28.5	21.0	35.7	4.5	2.5	3.0

* $\frac{\text{Hematocrit I} - \text{Hematocrit II}}{\text{Hematocrit II}} \times 100$

† $\frac{\text{Control Plasma Volume, \%} \times \text{Control Plasma Protein, Gm./100 Cc.}}{\text{Control Plasma Volume, \%} + \text{Percentage Increase}}$

11. Kracke, R. R., and Parker, E. P.: Textbook of Clinical Pathology, ed. 2, Baltimore, Williams & Wilkins Company, 1940, p. 142.

12. The preparation used was Mercupurin, supplied by Campbell Products, Inc.

one hour.[18] Several attempts were made to measure the increase in plasma volume by the spectroscopic method using Evans blue. Because of the hyperlipemia present in association with the hypoproteinemia, measurement of the plasma volume was unsuccessful by this method.

necessary to assume that hepatic damage plays an important role in this depression. It is of interest that no patient in our series showed symptoms or signs of hepatomegaly.

Successful elimination of edema has been of great value to our patients. It has been especially

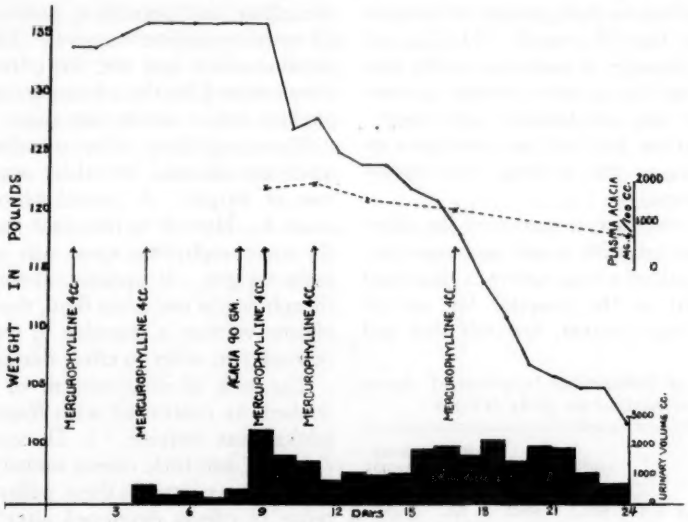

Chart 1.—Fluid balance in nephrosis; effects of acacia and mercurophylline. The solid line indicates body weight, the broken line acacia level in the plasma and the solid blocks urinary volume.

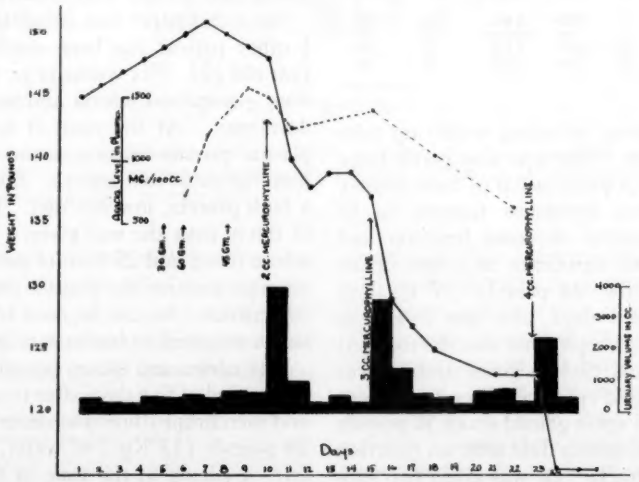

Chart 2.—Fluid balance in nephrosis; effects of acacia and mercurophylline. The patient was a woman 25 years old. The initial value for total protein was 4.30 Gm. per hundred cubic centimeters. The solid line indicates body weight, the broken line acacia level in the plasma and the solid blocks urinary volume.

Since the increase in plasma volume is sufficient to explain the changes in the plasma protein concentration after injection of acacia, it is unnecessary to assume that hepatic damage plays an important role in this depression. It is of interest that no patient in our series showed symptoms or signs of hepatomegaly.

Successful elimination of edema has been of great value to our patients. It has been especially valuable to the patients with massive edema, who within from ten days to two weeks are changed from waterlogged, bedridden patients to ambulatory ones, able to return home and resume most of their ordinary daily activities. Chart 1 illustrates these results. The patient whose course

13. Taran, A., and Eckstein, A.: Standardization of Congo Red Test for Amyloidosis, Am. J. M. Sc. **203:** 246, 1942.

is outlined was a schoolgirl who had been observed for several weeks in the hospital while she was on a regimen of a high protein, low salt diet and restricted intake of fluids. She showed no tendency to lose her edema during this period.

When treatment with acacia and mercurophylline was started, there was an immediate and progressive loss of edema fluid, so that in fourteen days this patient lost 31 pounds (14 Kg.) of water. At that time she became essentially free of edema, although her plasma protein concentration was 3.98 Gm. per hundred cubic centimeters. This patient has had no recurrence of edema to the time of this writing, after twelve months' observation.

Chart 2 is another demonstration of the effectiveness of treatment with acacia and mercurophylline. The patient whose course is described had been treated in the hospital for several months with a high protein, low salt diet and

TABLE 3.—*Effects of Intravenous Injections of Acacia and Mercurophylline on Body Weight*

Case	Edema	No. of Injections	Acacia Dose (Total, Gm.)	Period of Treatment	Body Weight Before Acacia, Lb.	Body Weight After Acacia, Lb.
1. N. P. (F)	3+	1	120	8 days	113	107
2. M. V. (F)	4+	6	325	8 wk.	169	110
3. V. W. (F)	3+	3	270	4 wk.	99	82
4. M. J. (M)	4+	1	90	2 wk.	136	102
5. T. C. (M)	No edema	2	180	9 days	...	...
6. A. H.	3+	3	270	5 wk.	146	125
7. I. H. (M)	1+	1	80	10 days	84	81
8. C. G. (M)	4+	2	120	3 wk.	61	56
9. D. D. (M)	1+	2	120	3 wk.	67	69

with various diuretics, including acidifying salts and mercurophylline. She was also given large doses of nephritin (a preparation of fresh kidney substance containing hormones thought to be associated with control of renal function and metabolism) without significant reduction of the edema fluid. She lost 38 pounds (17 Kg.) of water within sixteen days after the treatment with acacia and mercurophylline was started. At that time her plasma protein concentration was 3.94 Gm. per hundred cubic centimeters. About one month later she again gained about 10 pounds (4.5 Kg.) additional edema fluid after an infection of the respiratory tract. She was given two subsequent treatments, after which she became free of edema and remained so.

Table 3 shows the effects of acacia and mercurophylline on the edema of all the patients in our series. The loss of edema after this treatment was satisfactory in all the adult patients (cases 1 through 6). It appears certain that these patients would not have lost their edema had the acacia not been followed immediately by the mercurophylline. This fact is demonstrated in charts 1 and 2. Not only did these patients show no loss in edema, but there was a general tendency for the body weight to increase when acacia alone was administered. This increase occurred in spite of the obvious mobilization of water by the acacia, demonstrated by the reduction in the hematocrit reading. Diuresis was immediate and persistent, however, as soon as the mercurophylline was given. That the mercurophylline alone was not the effective agent was demonstrated by the administration of mercurophylline before acacia was given.

Mercurophylline alone usually resulted in a moderate diuresis, but there was no persistent loss of weight. A typical example is seen in chart 1. Here it is seen that the total effect of the mercurophylline alone was a slight gain in body weight. It appears, therefore, that even though acacia mobilizes fluid, thus increasing the plasma volume, a stimulus to renal excretion is necessary in order to effect diuresis.

The lack of improvement of the 3 children studied, as contrasted with improvement of the adults, was striking. I. H. and C. G. (cases 7 and 8) had little edema initially. A slight loss of edema occurred in these patients, but a recurrence of edema developed after their discharge from the hospital. D. D. (case 9) showed not even temporary loss of edema, even though his edema and ascites were massive.

Since this paper was submitted for publication, 1 other patient has been studied. She is a 14 year old girl. Six weeks prior to her hospitalization, generalized edema and massive proteinuria developed. At the time of her admission, her plasma protein concentration was 4.1 Gm. per hundred cubic centimeters. She was treated with a high protein, low salt diet. During the course of thirty days she was given a total of 4 liters of whole blood and 25 Gm. of serum albumin in an attempt to raise the plasma proteins and reduce the edema. As can be seen from chart 3, there was a progressive increase in body weight.

Her edema and ascites became extreme. Within a period of five days after treatment with acacia and mercurophylline was started, this patient lost 29 pounds (13 Kg.) of water, and she has been free of edema to the time of this writing. The proteinuria has continued.

The plasma acacia was measured for all patients. In general, the percntage of increase in plasma volume was proportional to the quantity of acacia injected per kilogram of body weight. As seen in table 1, the plasma acacia varied from 1 to 2.7 Gm. per hundred cubic centimeters. There was a gradual decrease in the plasma acacia after the first two days. However, small quantities of acacia were still demonstrable in

the plasma for several months after the last administration.

The Urinary Excretion of Acacia.—The excretion of acacia in the urine was determined for most of our patients. By some, measurable amounts of acacia were continuously excreted twenty to thirty days after the last injection. From 1 patient 38 per cent of the 135 Gm. injected was recovered in the urine in a thirty day collection period. The fact that on the average about 1 Gm. per day was still being recovered at the end of the collection period suggests that a much larger percentage of acacia might have been recovered had the period of collection been extended.

On the other hand, 1 of the patients most severely ill showed a progressive decrease in the urinary excretion of acacia during a collection period of fifteen days, so that after twelve days no acacia was found in the urine for the remainder of the period. For both of the patients cited the clinical results were excellent. In neither was there a parallel change in the urinary excretion of protein. Table 4 summarizes the data on the urinary excretion of acacia.

The degree of proteinuria varied considerably among the patients studied. The magnitude for a given patient, however, was relatively uniform. Comparison of the total protein excreted in the urine in four day periods showed no consistent changes in the control period or in the period during which mercurophylline and acacia were administered.

Complications of Acacia Therapy.—The most common complications of the treatment were a mild fever and, occasionally, a chill. Some of the patients vomited several times after the injection was completed. This type of reaction was minimized and sometimes apparently prevented by the administration of acetylsalicylic acid and ephedrine when the treatment was started.

In 1 patient (case 3) epistaxis developed after treatment on two occasions. At the time of the epistaxis his prothrombin time was 58 per cent of normal. The epistaxis stopped shortly after the intramuscular administration of a synthetic vitamin K preparation.[13a] The prothrombin time showed a drop of 10 per cent to 25 per cent in several other patients for whom this determination was made before and after injection of acacia. However, there were no hemorrhagic manifestations in any of the other patients. These were the only complications observed during the course of these experiments.

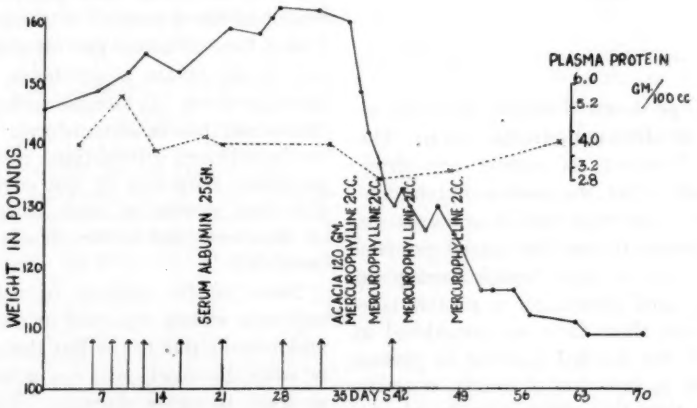

Chart 3.—Fluid balance in nephrosis; effects of blood transfusions, mercurophylline and acacia. The solid line indicates body weight; each long arrow indicates a transfusion of 500 cc. of whole blood, and the broken line indicates the total plasma protein concentration.

TABLE 4.—*Urinary Excretion of Acacia After Intravenous Injection*

Case	Acacia Injected, Gm.	Acacia Recovered, Gm.	Recovery, Percentage	Period of Collection, Days
M. V.	135	50.8	38	30
J. W.	90	10.9	12	12
M. J.	90	12.6	14	15
I. H.	80	8.8	11	11
W. C.	120	6.6	5.5	10

Distribution of Acacia in Body Tissues.—One patient who had hypoproteinemia and edema as a complication of a chronic inflammatory effusion of the pleural and peritoneal cavities was treated with acacia. He died fifty days after the injection of 120 Gm. of acacia. The distribution of

13a. The preparation used was Synkayvite, a water-soluble naphthohydroquinone with pronounced vitamin K activity, the sodium salt of 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester.

acacia found in his tissues and bile are listed in table 5.

COMMENT

That acacia is a useful drug in the treatment of resistant nephrotic edema seems unquestionable. The major objection to acacia, namely, its effect on the plasma proteins and on the liver, bears careful analysis. There seems no doubt that if sufficiently large doses of acacia are administered they may produce undesirable effects. The same is true, however, of almost any drug. The rapidity with which the plasma protein concentration drops after injection of acacia seems to eliminate damage to the liver as its primary cause. Other forms of acute hepatic damage do not cause such rapid depression in protein concentration. When these facts are considered in connection with the decided increase in plasma volume incident to injection of acacia, it seems almost certain that this depression in plasma protein is primarily the result of dilution. The point of view that acacia in the liver inhibits regeneration of plasma protein has not been established. The fact that in some nephritic patients plasma proteins are not built up to normal levels for many weeks after acacia therapy cannot be admitted as proof, since one often can make the same observation concerning nephritic patients who have never received acacia therapy. Further, in some patients plasma proteins are regenerated rapidly even after acacia therapy. Such an example is illustrated by table 6, concerning V. W. (case 3 in our series).

TABLE 5.—*Distribution of Acacia in Body Tissues (Fifty) Days After Intravenous Injection*

Tissues	Concentration, Percentage	Weight of Organ, Gm.	Total Acacia, Gm.
Brain	0	1,275	0
Heart	0.093	225	0.20
Stomach	0.234	?	?
Lung	0.335	900	3.19
Kidney	0.516	390	2.01
Liver	2.070	1,200	24.80
Spleen	5.450	150	8.17
Blood	0.846		
Bile	0.218		
Total recovery			38.37

TABLE 6.—*Regeneration of Plasma Proteins After Acacia*

Date	Plasma Protein, Gm. per 100 Cc.	Albumin / Globulin	Plasma Acacia, Mg. per 100 Cc.
8/20/43	2.37	0.30	1,618
8/24/43	3.16	0.91	1,326
8/31/43	3.98	0.63	853
9/11/43	4.93	0.81	
10/ 2/43	5.50	1.05	
11/ 2/43	6.53	1.72	

It is of interest to note the quantities of acacia given in the reported experiments in which patients were found to have enlarged tender livers and in the experiments on dogs in which the livers were four to five times normal size. The patient reported by Faulkenstein and Jackson [2b] received 705 Gm. of acacia, which was equivalent to 24.5 Gm. per kilogram of body weight. In the experiments on dogs reported by Yulie and Knutti,[3a] the animals received from 28 to 41 Gm. of acacia per kilogram of body weight. The quantity of acacia given in our series varied from 1.45 to 5.94 Gm. per kilogram, with an average of 3.18 Gm. per kilogram of body weight. There seems to be no necessity for the administration of such enormous quantities of acacia as 20 to 40 Gm. per kilogram of body weight in the treatment of nephrotic edema. If 1 or 2 Gm. of acacia per kilogram are injected, one should obtain a significant increase in the plasma volume. A diuretic such as mercurophylline should then be administered. This procedure can be repeated several times if necessary. If no persistent reduction in the edema fluid occurs after that amount of acacia, there appears to be no assurance that further acacia therapy will be beneficial.

Some of the failures of acacia therapy in nephrotic edema reported in the literature were undoubtedly due to the fact that the mobilization of water by acacia was not a sufficient stimulus in itself to cause diuresis. This fact was repeatedly demonstrated in our experiments. The reason for this result is not clear. Although the nephrotic kidney handles chloride essentially in the same way as does the normal one,[14] the exact relation between renal damage in glomerulonephritis and retention of salt and water is still obscure.[15] The edema fluid in persons with nephrosis is essentially a colloid-free filtrate of plasma.[16] As acacia mobilizes this edema fluid, thus increasing the plasma volume, it appears certain that the associated sodium is simultaneously mobilized and presented to the kidney. However, because of the composition of the edema fluid, there need be no change in the concentration of sodium and chloride in the plasma after acacia is administered. It may be true that

14. Loeb, R. F.; Atchley, D. W.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On the Mechanism of Nephrotic Edema, J. Clin. Investigation **11**:621, 1932.

15. Peters, J. P.; Salt and Water Metabolism in Nephritis, Medicine **11**:435, 1932.

16. Loeb and others.[14] Peters.[15]

the blood volume in patients with nephrotic edema is more nearly normal after mobilization of water by acacia than before, so that hypervolemia need not actually occur. In this event an additional stimulus such as mercurophylline might be necessary for diuresis. Decreased blood volume in patients with stabilized or increasing nephrotic edema has been reported as characteristic.[17] The patients in this series for whom the blood volume was measured showed values as much as 24 per cent below that expected for their ideal weight (Gibson and Evans.)[18]

The ineffectiveness of acacia and mercurophylline in the treatment of nephrotic children as contrasted with the effectiveness in treatment of nephrotic adults in this group of patients is unexplained.

CONCLUSIONS

The clinical and physiologic effects of the intravenous injection of acacia have been studied on 8 patients with the nephrotic syndrome of chronic glomerular nephritis, on 1 patient with hyperproteinemia and on 1 patient with hypoproteinemia and edema complicating a chronic polyserositis.

A simultaneous reduction in the plasma protein concentration and in the hematocrit reading was constantly observed after the injection of acacia. By means of the changes in the hematocrit reading, the degree of depression of the plasma protein concentration was predicted. This predicted depression showed close correlation with the observed depression. The reduction in plasma protein concentration, therefore, is considered to be primarily the result of an increase in plasma volume at the expense of the edema fluid, incident to the hydrophilic effect of the circulating acacia.

No evidence was found to indicate that the injected acacia inhibited regeneration of plasma protein. No serious complications were observed.

Concentrations of acacia in the tissues of 1 patient who died fifty days after injection of acacia were studied. The greatest concentrations were found in the liver and in the spleen.

No beneficial effect was observed from the use of this therapy on the children studied in this series.

Intravenous injections of acacia, when followed by mercurophylline injection, proved a valuable aid in eliminating nephrotic edema in the adult patients studied.

17. Waterfield, R. L.: Changes in Blood Volume in Patients with Edema of Renal Origin, J. Clin. Investigation **9**:589, 1931. McClure, W. B.; de Takáts, C. B., and Hinman, W. F.: Mechanism of Edema of the Renal Type, Arch. Int. Med. **51**:819 (June) 1933.

18. Gibson, J. G., and Evans, W. A.: The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, J. Clin. Investigation **16**:317, 1937.

RECURRENT MENINGOENCEPHALITIS DUE TO THE VIRUS OF LYMPHOGRANULOMA VENEREUM

DAVID W. SCOTT JR., M.D.
Surgeon, United States Public Health Service; Clinical Director, United States Marine Hospital
CHICAGO

The concept of lymphogranuloma venereum as a systemic infection rather than a local one is of fairly recent origin. Beginning with the report of Durant, Nicholas and Favre [1] in 1913, evidence has accumulated in support of this view. Van Rooyen and Rhodes [2] stated that, in addition to the more frequent involvement of genitalia and regional lymph glands, lymphogranuloma venereum may manifest itself by involvement of the throat, with inflammation of the tonsils, ulcerations or angina, by fever, with headaches and other pyrexial disturbances, by cutaneous rashes, by various forms of articular involvement, by generalized involvement of the lymph nodes, with splenomegaly and hepatomegaly, by granulomatous conjunctivitis, by epididymitis and by meningoencephalitis. In 1936 von Haam and D'Aunoy [3] reported the isolation of the virus from the spinal fluid of 2 patients during the acute stage of the infection, when the cerebral manifestations consisted mainly of headaches. Rajam [4] reported a case of lymphogranuloma venereum in which death from meningoencephalitis occurred after surgical intervention on the buboes. Sabin and Aring [5] isolated the virus from the spinal fluid of a patient showing pronounced cerebral changes and also from the inguinal lymph node six weeks after the onset of the acute phase of the illness. They also found further proof, in complement fixation studies, of the etiologic relation of the virus to the illness encountered. Zarafonetis [6] published a report of 2 cases, in 1 of which the virus was isolated from the inguinal lymph node five months after the onset of the illness and the serum was found to fix the complement. Of interest in this case, also, was the colloidal gold curve, which showed a persistent, strongly positive first zone reaction.

In the case to be presented in this paper an attempt was made to isolate the virus from blood, from spinal fluid and from the originally involved inguinal lymph nodes. Numerous serial intracerebral passages in mice were tried with both the spinal fluid and the blood but without success in recovering the virus. The specimen of serum, however, was found to fix the complement in significant dilution with lymphogranuloma venereum antigen as well as with psittacosis antigen, and fixation of complement was also obtained with spinal fluid. Also of interest in this case is the colloidal gold curve, which is similar to that shown in the case reported by Zarafonetis [6]; that is, there is a strongly positive first zone reaction.

REPORT OF A CASE

V. P., a 21 year old white man, was admitted to the United States Marine Hospital Chicago, on Aug. 9, 1944, with the chief complaint of "double vision." At that time he stated he had been in good health until January, when bilateral buboes developed. These were incised, and he was given sulfonamide compounds, with an apparently uneventful recovery. In April, after he had had sexual contact with a "dark-skinned" Puerto Rican girl, swelling of the inguinal lymph nodes again developed bilaterally. This was followed within a week to ten days by the gradual development of headache and malaise followed by chilly sensations and fever. The headache became progressively more severe, and he noticed twitching of the muscles of his face. On May 9 he was admitted to the United States Marine Hospital, Boston. Physical examination at that time

1. Durant, Nicholas and Favre: Lymphogranulomatose inguinale subaigne; d'origine genitale probable, pent-etre venerienne, Bull. Soc. méd. d'hóp. Universitaires de Québec **35**:274-288, 1913.

2. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, pp. 176-196.

3. von Haam, E., and D'Aunoy, R.: Infectivity of Spinal Fluid in Lymphogranuloma Inguinale, J. A. M. A. **106**:1642-1643 (May 9) 1936.

4. Rajam, R. V.: Report of Fatal Case of Lymphogranuloma Inguinale from Meningoencephalitis, Brit. J. Ven. Dis. **12**:237-241, 1936.

5. Sabin, A. B., and Aring, C. D.: Meningoencephalitis in Man Caused by Virus of Lymphogranuloma Venereum, J. A. M. A. **120**:1376-1381 (Dec. 26) 1942.

6. Zarafonetis, C. J. D.: Meningoencephalitis in Lymphogranuloma Venereum, New England J. Med. **230**:567-573, 1944.

showed twitching of the muscles of the entire face, a few small palpable lymph nodes in the neck, bilateral inguinal scars from previous buboes and, on either side, a firm inguinal lymph node about the size of a hickory nut. There were no penile lesions. There was no stiffness of the neck and no Kernig sign. A tentative diagnosis of meningococcic meningitis was made. The spinal fluid showed 250 cells, mostly lymphocytes; the pressure was 150 mm. of water and the fluid clear. Culture of the spinal fluid showed no growth. Values for proteins and chlorides in the spinal fluid were normal.

TABLE 1.—*Summary of Results of Examinations of the Spinal Fluid During June 1944*

	6/5/44	6/11/44	6/15/44	6/21/44	6/24/44
Color	Color-less	Color-less	Color-less	Color-less	Color-less
Turbidity	Clear	..	Clear	Clear	..
Protein (Mg./100 Cc.)	44	80	38	52	..
Sugar (Mg./100 Cc.)	40	47	50	60	50
Cell count	270	166	62	40	55
Polymorphonuclear leukocytes	70	25	0	0	12
Mononuclear leukocytes	30	70	100	100	88
Ritz reaction	Negative				
Wassermann reaction	Negative				
Colloidal gold curve	Negative				
Red blood cells	0				
Growth in culture	None	None	None	None	None
Growth in smear	None	None	None	.....	None

Results of urinalysis and of studies of the blood during this same time were essentially normal, Wassermann and Kline reactions of the blood were negative.

Wassermann and Davies-Hinton reactions of the blood were negative. Culture of the blood showed no growth. The Frei test elicited a positive reaction. The blood count was essentially normal. Under treatment with sulfadiazine, the temperature returned to normal within three days. However, there were several recurrences of fever during his stay in the hospital. At the time of his discharge on May 29, he appeared to have recovered.

After leaving the Boston Marine Hospital, the patient went to Minneapolis, where on June 5 there was a recurrence of the intense headache and vomiting. He entered a hospital on that date, and a diagnosis was made of recurrent meningococcic meningitis, based on clinical findings. Numerous spinal taps were performed, the results of which, along with other laboratory data, are summarized in table 1.

He was again treated with sulfonamide drugs and became asymptomatic and was discharged on June 26. He had remained at home about one week when a stiff neck, headache and vomiting developed and he was hospitalized at another hospital, where he was again given a course of sulfonamide drugs, with prompt symptomatic recovery. One week later he had a similar attack and returned to the hospital. His complaints on this admission were intermittent headaches and stiffness in the back of his neck and in his back. He was said at times to become noisy, moaning and crying. It was reported by the eye, ear, nose and throat consultant that the patient had an involvement of the third cranial nerve, with diplopia, and some bilateral papilledema. Results of examination of the spinal fluid were reported as follows: Kline reaction positive (2 plus), Kolmer-Wassermann reaction negative, Nonne reaction positive, fluid cloudy, smear negative for bacteria, cells 6 and colloidal gold curve 5555543211. He again became asymptomatic after the administration of sulfonamide drugs and was discharged to report to the United States Marine Hospital, Chicago, for further observation and treatment.

Physical examination at the time of his admission to the Chicago Marine Hospital showed the head to be normal. The pupils were equal and regular and reacted to light and in accommodation; the scleras were clear; there was no demonstrable muscular imbalance and no nystagmus or lid lag, and the fundi appeared to be within normal limits. The neck was freely flexible. No enlarged nodes were noted. There were bilateral inguinal scars with small hard inguinal lymph nodes palpable bilaterally. Reflexes and other neurologic signs were normal throughout, with the exception of a questionable Babinski reflex on the right. There was noted a slight hesitancy of speech, which the patient stated had not been present prior to his illness. Laboratory studies showed normal urine. There were 5,100,000 red blood cells, 14.6 Gm. of hemoglobin, 5,600 white cells, 38 per cent lymphocytes, 5 per cent monocytes, 2 per cent eosinophils, 50 per cent neutrophils and 5 per cent stab forms. The Wassermann and Kahn reactions of the blood for syphilis were negative. In the blood, the total protein was 7.15 Gm. per hundred cubic centimeters, albumin 3.6 Gm. and globulin 3.5 Gm. Cultures of nasopharyngeal materials showed no growth of meningococci. A spinal puncture performed on August 12 revealed a total cell count of 91, with 96 per cent monocytes and 4 per cent polymorphonuclear leukocytes. The Pandy reaction was positive (4 plus). Culture of the spinal fluid showed no growth, and the Kahn and the quantitative Kolmer-Wassermann reactions were negative in all dilutions. The total protein was 156 mg. per hundred cubic centimeters, chlorides 620 mg. and sugar 60 mg., and the colloidal gold curve was 5555543100. On August 26 a second spinal puncture was done, and the report showed a 4 plus Pandy reaction, a cell count of 4,

TABLE 2.—*Summary of Results of Examinations of the Spinal Fluid in Chicago Marine Hospital*

	8/11/44	8/26/44	11/17/44
Cell count	96% Mononuclear leukocytes, 4% polymorphonuclear leukocytes	4 Mononuclear leukocytes	0
Pandy reaction	4 plus	4 plus	Trace
Growth in smear	None	.....	None
Growth in culture	None	.....	None
Kahn reaction	Negative	.....	.....
Quantitative Kolmer-Wassermann reaction	Negative	Negative	Negative
Total protein	156 mg./100 cc.	61 mg./100 cc.	.....
Chlorides	620 mg./100 cc.	.....	.....
Sugar	60 mg./100 cc.	.....	.....
Colloidal gold curve	5555543100	5543510000	554211000

with monocytes predominating, a negative quantitative Kolmer reaction, 61 mg. of total protein and a colloidal gold curve of 5543510000. A specimen of this fluid, together with a sample of blood, was sent to Dr. John L. White at the laboratory of the Chicago Health Department for complement fixation tests for lymphogranuloma venereum. The complement was fixed with both the blood and the spinal fluid. The Frei test elicited a 1 plus positive reaction, but the control test

showed a positive reaction of about the same degree. The results of the tests made at this time are summarized in table 2.

On August 29 the patient suffered a recurrence of his former symptoms, complaining of severe headache, diplopia, stiff neck and vomiting. Treatment with sulfadiazine was started, with prompt symptomatic improvement. The drug was continued at the rate of 1 Gm. every four hours, day and night, for a period of one week and then four times a day for five weeks.

On September 2 specimens of blood, serum and spinal fluid were submitted to the National Institute of Health for virus and complement fixation studies. The virus was not isolated. Complement fixation was confirmatory. A second specimen of spinal fluid was sent to Dr. White at the Chicago Health Department on October 23, and again a complement fixation for lymphogranuloma venereum was reported. Efforts to isolate the virus from the excised inguinal lymph node were unsuccessful. Microscopic studies of this node showed a chronic, nonspecific fibrous lymphadenitis.

On October 25 the patient, at that time being entirely asymptomatic, was discharged to the status of an outpatient. He was seen again on November 14, when he stated that he felt entirely well and had had no recurrences of any sort. A spinal puncture was performed on that date, and the report was as follows: The quantitative Kolmer reaction was negative in all dilutions; no cells were found; there was a trace of a Pandy reaction, and the colloidal gold curve was 5542211000.

COMMENT

A review of the literature reveals 6 previously reported cases of meningoencephalitis presumably due to the virus of lymphogranuloma venereum. The virus itself was isolated in 4 of these cases—in 3 from the spinal fluid and in 1 from an inguinal lymph node only. Further confirmation was obtained in 2 of these cases by complement fixation studies of the serum.

In the case presented in this paper the virus was not isolated. This failure to isolate the virus may have been due in part to the length of time elapsed before this study was attempted and also to the considerable amount of treatment with the sulfonamide drugs which this man had previously received. Virus studies were performed by Dr. Dorlund J. Davis, of the National Institute of Health, Bethesda, Md. Dr. Davis reported that numerous serial intracerebral passages in mice were tried with both the spinal fluid and the blood but without the recovery of any specific virus. The specimen of serum, however, showed complement fixation in significant dilution with lymphogranuloma venereum antigen, as well as with psittacosis antigen.

The report of the microscopic examination of the excised inguinal lymph node stated that the capsule was thickened and fibrosed. Fibrous bands extended from the capsule and penetrated into the cortex. Within the medulla there were also thick fibrous deposits. The follicles were obvious and were composed primarily of small lymphocytes. Reticulum cells were relatively sparse. Fibroblastic activity in the follicles was present within the medulla. Reticulum cells were increased in number. Blood vessels were thickened. No indications remained that there was a specific infection.

Isolation and identification of the virus is too elaborate and slow a procedure to use routinely for diagnostic purposes. It is necessary, therefore, to depend on some other procedure for laboratory confirmation. The complement fixation test thus becomes a valuable aid in early diagnosis of infections with the virus of the lymphogranuloma-psittacosis group. Differentiation between these conditions must depend on clinical observations, since with the antigens now available it is not possible to differentiate these closely related viruses. Employment of the complement fixation test on spinal fluid in this condition has not previously been reported, and this study was facilitated by the use of this procedure by Dr. John L. White, of the laboratories of the Chicago Health Department.

The value of the Frei test as a diagnostic aid is questionable. Although the original test performed in Boston was reported to have elicited a positive reaction, a subsequent test in this hospital was doubtful, and there have been many instances of negative reactions to Frei tests in which the clinical evidence was overwhelmingly in favor of lymphogranuloma venereum. In the case reported by Zarafonetis,[6] the reaction to the Frei test was negative at the time the virus was recovered from an excised lymph node, although it subsequently became positive.

The results of examinations of the spinal fluid in this case are of interest, but, with the exception of the complement fixation, not diagnostically specific. The colloidal gold curve was persistently of the first zone, dementia paralytica type, and the total protein was slightly increased (156 mg. per hundred cubic centimeters). These observations resemble those in the case reported by Zarafonetis,[6] but the values are less extreme. For one specimen the Kline reaction was reported 2 plus positive, but for all subsequent specimens this, as well as all other reactions for syphilis, was negative.

The response of this condition to sulfonamide therapy appeared to be satisfactory. With each of his attacks the patient promptly became asymptomatic on institution of this treatment. The recurrences are believed due to the fact that the drug was not continued over a long enough period. After a course of treatment with sulfa-

diazine lasting approximately six weeks the patient was apparently entirely recovered. It would appear from this case, therefore, that rather prolonged sulfonamide therapy is necessary to effect a cure in this condition.

SUMMARY

A review of the literature presented evidence that the virus of lymphogranuloma venereum can act as the causative agent in meningoencephalitis.

A case of meningoencephalitis with evidence incriminating this virus as the probable cause was observed.

The value of various laboratory procedures as diagnostic aids was considered.

Treatment with the sulfonamide drugs was found to be effective but must be continued for a considerable period after the patient becomes asymptomatic to prevent recurrence.

Book Reviews

Clinical Heart Disease. By Samuel A. Levine, M.D., F.A.C.P. Third edition. Price, $6. Pp. 462, with 157 illustrations. Philadelphia: W. B. Saunders Company, 1945.

The appearance of the third edition of this popular book is welcome indeed, for it continues to fulfil the need for a simple, readable account of the common problems of heart disease. Its style is forceful and expresses the experiences and convictions of the author. It demonstrates the qualities that have made him so excellent a clinical teacher. The sections on the surgical treatment of patent ductus arteriosus and on the chemotherapy, including treatment with penicillin, of subacute bacterial endocarditis have been amplified. A summary of studies on the heart in scleroderma, on rupture of valves and on the heart in Addison's disease has been added. The section on electrocardiography has been expanded greatly, and special reference has been made to the precordial leads. It is apparent that the author has followed the views of Wilson and his school closely in the latter development, and at times the reviewer feels that the subject has been made more complex than necessary for the average practitioner, for whom this book is intended. The section on the arrhythmias continues to be lucid and valuable. The discussion of phonocardiology is unnecessarily complex for the ordinary reader, and there is little purpose in illustrating the cardiac sound tracings.

The author is at his best when he is describing the clinical picture and the management of heart disease, drawing on his extensive experience. He is less so when he delves into the genesis and physiologic disturbances associated with these diseases. There are many statements in this category with which the reviewer cannot agree.

This book is an outstanding contribution to the literature concerning heart disease, which no physician interested in the subject can afford to overlook.

Doctors at War. Edited by Morris Fishbein, M.D. Price, $5. Pp. xiii + 418, with 82 illustrations. New York: E. P. Dutton & Co., Inc., 1945.

This book has been written by sixteen experts under the editorial leadership of one. It describes doctors at war and how their different talents have been amalgamated for the benefit of the nation.

The contents are particularly well organized and comprehensive. There are chapters which outline the medical side of Selective Service, procurement and assignment, the practice of preventive medicine in the army and the accomplishments of the United States Public Health Service. There are chapters which tell what the doctor in active service actually does in different theaters of operation when he is an officer in the army, navy or air forces. There is a chapter which discusses the problem of convalescence and rehabilitation and another which deals with the Veterans' Administration. There are chapters which sketch the work of the Red Cross in making blood substances available to the wounded and how investigations were carried out under the National Research Council.

One of the most interesting features is the manner in which the different chapters are written. Each one is like a presentation to a medical society, restrained, unemotional, clear and factual. Yet any one reading between the lines feels the strength of American medicine, its ideals and its unselfishness.

The volume is an important one. All physicians will take pride in such an historic document.

Patients Have Families. By Henry B. Richardson, M.D., F.A.C.P., associate professor of clinical medicine, Cornell University Medical College; attending physician, New York Hospital; visiting physician, Bellevue Hospital. Cloth. Price, $3. Pp. 408. New York City: The Commonwealth Fund, 1945.

This work is another of the excellent contributions of the Commonwealth Fund and represents the recognition of a hitherto neglected difficulty. It deals with the effect of the patient's illness on his family. It describes the effect of the family and the environment on the illness of the patient. It points out the proper attitude of the physician and the psychiatrist in the solution of the problem. The medical social worker is given a place in the picture. The author points out the opportunity for research in the study of the family unit, and he gives numerous examples of professional technics to be used in meeting the problems.

It seems obvious that this book must produce a variety of reactions in its readers. By the social worker, the psychologist and the highly specialized psychiatrist the book will doubtless be received as the finger that points toward the proper solution of the problem. To many less sympathetic readers, the method will seem to perpetuate and worsen a condition that has grown out of a too restricted medical interest.

At any rate, the book plainly points out that the medical profession is confronted with a situation that it may well have created and which must be met. Whether the author's method of meeting it is the correct one remains for the future to decide.

Progress in Internal Medicine

INFECTIOUS DISEASES

ELEVENTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

HOBART A. REIMANN, M.D.
PHILADELPHIA

(Concluded from Page 129)

DISEASES OF THE GASTROINTESTINAL TRACT

Epidemic Nausea, Vomiting and Diarrhea (Viral or Viroid Dysentery?).—Report is made [146] of a widespread mild contagious disease characterized by symptoms of a deranged gastrointestinal tract. For several reasons the disease has not attracted much medical attention: First, like the common cold, it is mild and its victims are usually ambulatory; second, its manifestations are not so obvious as those of the cold, and, third, the symptoms, because of their nature, are usually not discussed in casual conversation. It is probably worldwide in distribution, and its mode of dissemination suggests the cause to be a filtrable agent which passes from person to person as in air-borne infections. In tests made on volunteers who inhaled filtrates of garglings and of stools, presumptive evidence was obtained that the causative agent is filtrable and is air-borne, but the experiments were made with fresh material, by necessity during an epidemic period, so that final proof is still needed.[147] The mere absence of a demonstrable bacterial cause does not prove that a virus is the cause. The etiologic problem at present is as unsettled as that of viroid, or viral, pneumonia, and the matter of naming the disease is similarly confused. It can hardly be called gastroenteritis without evidence of actual inflammation of the tract. The name "epidemic nausea, vomiting and diarrhea" is not wholly satisfactory either; it is cumbersome, and one or two of the named symptoms may be absent in different patients. The term "viral, or viroid, dysentery" is presented for consideration. The word "dysentery" appropriately means difficulty with the bowel, and "viral or viroid" suggests a filtrable virus as the cause. The disease would thus take its place among the infectious diseases called bacillary dysentery and amebic dysentery.

Incidentally, Rosenow, in his usual manner,[148] obscures the issue by introducing a streptococcus "having special affinity for the gastrointestinal tract" which in its filtrable form causes the disease.

Epidemic Jaundice, Infectious Hepatitis.—Epidemic jaundice, or infectious hepatitis, is called one of the new epidemic diseases of the current war. It has indeed been a serious problem, so much so as to interfere at times with military operations.[118] The problem of its identity with various other forms, namely, vaccine jaundice or homologous serum jaundice, arsenotherapy jaundice and others, is still unsettled because of their clinical and pathologic similarities. The chief difference is in the length of the incubation period, but, according to Oliphant,[149] patients who recovered from serum jaundice are immune to inoculation with serum from patients with infectious hepatitis or with icterogenic yellow fever vaccine, suggesting the identity of these diseases. Immunity lasts twelve to eighteen months. MacCallum [150] noted jaundice in volunteers receiving injections of serum from patients who had postarsenotherapy jaundice. According to Havens,[151] the icterogenic agent of infectious hepatitis can be transmitted in serial passage in human volunteers. The agent, like that of postvaccinal jaundice and homologous serum jaundice, is durable and survives heat at 56 C. for

146. Reimann, H. A.; Hodges, J. H., and Price, A. H.: Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, J. A. M. A. **127**:1-5 (Jan. 6) 1945.

147. Reimann, H. A.; Price, A. H., and Hodges, J. H.: The Cause of Epidemic Nausea, Vomiting and Diarrhea (Viral Dysentery?), Proc. Soc. Exper. Biol. & Med. **59**:8-9 (May) 1945.

148. Rosenow, E. C.: Infectious Gastroenteritis: An Epidemiologic and Laboratory Study, Am. J. Digest. Dis. **11**:381-391 (Dec.) 1944.

149. Oliphant, J. W.: Infectious Hepatitis: Experimental Study of Immunity, Pub. Health Rep. **59**:1614-1616 (Dec. 15) 1944.

150. MacCallum, F. O.: Transmission of Arsenotherapy Jaundice by Blood: Failure with Feces and Nasopharyngeal Washings, Lancet **1**:342 (March 17) 1945.

151. Havens, W. P.: Properties of the Etiologic Agent of Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. **58**:203-204 (March) 1945.

thirty minutes. The same author and others [152] show that the virus is present in the blood, feces, nasopharyngeal washings and urine in the early stages and even before clinical symptoms appear. The latter point is reemphasized by Neefe and his associates,[153] who also report on several patients in whom clinical jaundice never appeared and for whom the diagnosis would have been missed had not laboratory evidence of hepatic dysfunction been obtained. One third of the victims of one epidemic did not become jaundiced.[154]

The mortality rate is generally believed to be about 0.2 per cent, but in a certain small percentage of cases there is evidence of residual injury to the liver. In a study on 200 patients [155] who still were not well five to nine months after the original attack, most of them were found to have symptoms which could be ascribed to neurosis, but about 12 per cent had evidence of persistent hepatic disease.

Treatment of jaundice with methionine was unsuccessful,[156] but experiences with gamma globulin were encouraging.[154] In one epidemic the incidence of hepatitis was said to have been significantly reduced by the intramuscular injection of gamma globulin in persons exposed to the infection. The substance seemed to prevent or ameliorate the disease if given during the incubation period.

Shigellosis.—In continued studies on acute diarrheal diseases, Hardy and Watt [157] reemphasize the great preponderance of mild attacks of simple diarrhea over so-called typical cases of bacillary dysentery. The number of cases of mild diarrhea is usually difficult to determine, since mild attacks are quickly forgotten. About 9 convalescent or passive carriers were found for each recognized case. In most instances the source of infection cannot be found.

Some order at last seems to be coming out of the classification of this group of bacteria, after the early work of Andrewes, Inman and Boyd and now after that of Weil and his associates.[158] In the Shigella paradysenteriae (Flexner) group there are eighteen patterns of agglutinative behavior, divided now into fourteen types with a single primary antigen and four with dual primary antigens.

Morton and Engley [159] critically review the evidence both favoring and discrediting the value of bacteriophage in the treatment of bacillary dysentery. Most clinical reports thus far published are inconclusive, but trial in animals seems to show its unmistakable therapeutic effectiveness. If either the sulfonamide compounds or streptomycin proves to be more effective, there will be no need for the use of bacteriophage or for immunotherapy.

In an attempt to provide a reliable method of prophylactic immunization, volunteers were given injections of a specific polysaccharide antigen of Flexner dysentery bacilli. [160] Agglutinins developed in the blood for the homologous strain and for other groups as well. The blood also contained protective antibodies. On the other hand, in a different study,[161] the agglutination test as usually performed was found to be an unreliable means of diagnosing infections with various members of the Shigella group, nor was it an index of immunity or susceptibility to infection. The agglutinin titer was usually higher for patients who shed bacilli in their feces but not sufficiently high, nor consistently so, to permit interpretation in individual cases.

152. Havens, W. P.; Paul, J. R., and VanRooyen, C. E.: Human Transmission of Infectious Hepatitis by the Oral Route, Lancet **1**:202-203 (Feb. 17) 1945. Findlay, G. M., and Willcox, P. R.: Transmission of Infected Hepatitis by Feces and Urine, ibid. **1**:212 (Feb. 17) 1945. MacCallum, F. O., and Bradley, W. H.: Transmission of Infective Hepatitis to Human Volunteers, ibid. **2**:228-229 (Aug. 12) 1944.

153. Neefe, J. R.; Stokes, J.; Reinhold, J. G., and Lukens, F. D. W.: Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers, J. Clin. Investigation **23**:836-855 (Sept.) 1944.

154. Stokes, J., and Neefe, J. R.: The Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin, J. A. M. A. **127**:144-145 (Jan. 20) 1945.

155. Benjamin, J. E., and Hoyt, R. C.: Disability Following Postvaccinal (Yellow Fever) Hepatitis: A Study of Two Hundred Patients Manifesting Delayed Convalescence, J. A. M. A. **128**:319-323 (June 2) 1945.

156. Pollock, M. R., and Harris, A. D.: Therapeutic Trial of Methionine in Infectious Hepatitis, Brit. M. J. **1**:399-401 (March 24) 1945. Higgins, G.; O'Brien, J. R. P.; Peters, R. A.; Stuart, A., and Witts, L. J.: Treatment of Infectious Hepatitis with Methionine, Brit. M. J. **1**:401-402 (March 24) 1945.

157. Watt, J., and Hardy, A. V.: Studies of the Acute Diarrheal Diseases: XIII. Cultural Surveys of Normal Population Groups, Pub. Health Rep. **60**:261-273 (March 9) 1945. Hardy, A. V., and Watt, J.: XIV. Clinical Observations, ibid. **60**:521-531 (May 11) 1945.

158. Weil, A. J.; Black, J., and Farsetta, K.: The Serological Types of Shigella Paradysenteriae (Flexner): II. Types with a Single Primary Antigen, J. Immunol. **49**:321-340 (Dec.) 1944; II. Types with Dual Primary Antigens: Practise of Typing; Discussion, ibid. **49**:341-351 (Dec.) 1944.

159. Morton, H. E., and Engley, F. B.: Dysentery Bacteriophage, J. A. M. A. **127**:584-591 (March 10) 1945.

160. Perlman, E.; Binkley, F., and Goebel, W. F.: Studies on the Flexner Group of Dysentery Bacilli, J. Exper. Med. **81**:349-358 (April) 1945.

161. Watt, J., and DeCapito, T. M.: Studies of Acute Diarrheal Diseases: XV. The Agglutination Test in Shigella Paradysenteriae Infections, Pub. Health Rep. **60**:642-650 (June 8) 1945.

Typhoid.—The use of streptomycin for typhoid has been discussed. According to Luippold, the standard subcutaneous method of vaccination against typhoid is superior to one tenth or one fifth of the dose given intracutaneously.[162] The latter is useful chiefly for elderly persons and for allergic persons, for whom the intracutaneous injection of small doses is safer.

Cholera.—In a series of papers in the December issue of the *Proceedings of the Society of Experimental Biology and Medicine,* Burrows and his associates report the isolation and properties of the endotoxin of the cholera vibrio. It is resistant to peptic and tryptic digestion and is possibly a phospholipid. Mice could be actively immunized with the toxin, but neutralization in vitro was not accomplished with either antibacterial or antiendotoxic serums known to be protective for mice. Mice could not be immunized against the intraperitoneal injection of endotoxin. Active immunity in human beings probably includes both antitoxic and antibacterial protection. A trial of streptomycin for the treatment of cholera is in order.

Ulcerative Colitis.—In considering types of ulcerative colitis on an etiologic basis, Bargen [163] still regards the streptococcus as a cause. With great numbers of streptococci usually present normally in the bowel and its wall and with no proof of their pathogenicity, he still advocates the use of an antistreptococcus vaccine and, what is even more futile, the removal of teeth and tonsils as foci of infection. No mention is made of the importance of psychic influence in the disease.

"Vincent's Infection."—According to dentists' views,[164] the etiology and epidemiology of ulcerative gingivostomatitis (Vincent's disease) are poorly understood. It is indeed an important disease, but it is not even known whether it is contagious or not or whether the spiral microorganisms usually associated with the disease are the cause. In one study, improvement of oral hygiene was therapeutically effective. In another, the technic for the isolation and cultivation of spirochetes from gingival lesions is described.

It is doubtful that sulfonamide compounds are of specific value in treatment.[165] The efficacy of penicillin therapy of the condition is uncertain, although one report,[166] made without control studies, is favorable. Patients treated with penicillin also received other hygienic oral treatment, which, as previously mentioned, is in itself effective. The use of penicillin was based on the analogy of its success in the treatment of syphilis and other spirochetal diseases, but just the fact that Vincent's spirochete is curly like other spirochetes is not reason enough to support the theory. At one time arsphenamines were used for the same reason, regardless of the fact that patients at times contracted Vincent's infections while undergoing intensive arsphenamine treatment for syphilis. Both penicillin and sulfonamide compounds may, indeed, influence favorably infections caused by gingival bacteria susceptible to their effects, but until further controlled study is made judgment should be reserved.

DISEASES OF THE CENTRAL NERVOUS SYSTEM

Poliomyelitis.—Toomey [167] warns against the use of sulfonamide therapy for poliomyelitis. It may be harmful.

In an epidemiologic study of poliomyelitis, reported by Pearson and his associates in the March number of the *American Journal of Hygiene,* specimens of stools from almost all people in a village where 1 case occurred were studied. Virus was recovered only from a son of the patient. Of 30 other persons associated with a patient, virus was recovered in the stools of only 3. Virus was not found in feces of farm animals or in flies, mosquitoes, rats or mice in the vicinity. It seemed that personal association was the principal factor involved in the spread of the virus. In an outbreak in a city, no evidence of sanitary defects was found, nor was any single source of food or milk incriminated. Mosquitoes, flies, rats and mice were not numerous. Virus was most often found among persons of a household in which a patient was present. Instead of a random scattering of cases, the distribution was concentrated about the

162. Luippold, G. F.: Typhoid Vaccine Studies: IX. Intracutaneous Versus Subcutaneous Vaccination for Initial Immunization, Am. J. Pub. Health **34**:1151-1162 (Nov.) 1944.

163. Bargen, J. A.: The Medical Management of Ulcerative Colitis, J. A. M. A. **126**:1009-1013 (Dec. 16) 1944.

164. Dunn, H. T., and Singleton, D. E.: Vincent's Infection—A Wartime Disease, Am. J. Pub. Health **35**:433-440 (May) 1945. Hamp, E. G.: Vincent's Infection—A Wartime Disease, ibid. **35**:441-450 (May) 1945.

165. Manson, W. W., and Craig, I. T.: Treatment of Vincent's Angina with Sulfathiazole, J. A. M. A. **127**:277 (Feb. 3) 1945.

166. Pearce, W. F., and McDonald, J. B.: Treatment of Ambulatory Patients with Penicillin Sodium, J. A. M. A. **128**:342-344 (June 2) 1945.

167. Toomey, J. A.: Treatment of Poliomyelitis, J. A. M. A. **126**:49 (Sept. 2) 1944.

source in a patient who served as a focus of infection. Others [168] found poliomyelitis virus in the oropharynx of nearly half of 23 patients but never after the third day of disease. Horstman and her associates [169] show that poliomyelitis virus persists in the feces of patients for variable periods after an attack but not permanently. Sixty-one per cent of patients excreted virus for two weeks after the onset of the disease, but the percentage gradually declined until only 12 per cent did after eight weeks. Only 1 excreted virus in the twelfth week.

From another study [170] the first direct evidence of the serving of contaminated food as a link in the chain of infection was derived. Food exposed to flies in homes where patients had the disease contained enough virus to cause mild forms of poliomyelitis in chimpanzees which ate the contaminated food. Poliomyelitis can obviously be transmitted in a number of ways.

In a study of noncontact persons during an interepidemic period, [171] tonsils and stools were collected from 136 persons. At least 5 of these persons harbored poliomyelitis virus, either in their tonsils or in their feces when the disease was not present in the community.

A case of a second attack of poliomyelitis in a woman of 32 is reported.[172] The first occurred thirteen years previously. Howe and Bodian [173] observed the apparent spontaneous infection of 2 chimpanzees with poliomyelitis. Melnick [174] isolated poliomyelitis virus from the blood of 4 of 10 infected monkeys.

While numerous earlier experiments show that mice given diets deficient in thiamine are more resistant to poliomyelitis, tests now show that riboflavin deficiency has a much less striking effect.[175] Incidentally, riboflavin-deficient mice are much less resistant to infections by organisms of the Salmonella group than are normally fed mice.[176] The apparent paradox of the fact that both immunity to viral infections and hypersusceptibility to bacterial diseases can stem from hypovitaminosis lacks explanation. Monkeys, unlike mice, are not more resistant to poliomyelitis when fed a thiamine-deficient diet.[177] Hypovitaminosis, therefore, is not related to increased resistance in all species of animals.

Studies by Schneider and Webster [178] illustrate how deceiving conclusions may be in regard to the effect of nutrition on resistance to infection if the results are not carefully controlled. Certain diets may indeed promote a higher survival rate in experimentally infected mice, but the differences noted depend largely on the genetic constitution of the mice used for study. The results of certain reported studies could not be duplicated in highly inbred strains of mice of known natural resistance.

During an epidemic of poliomyelitis in Iowa in 1943, 10 cases of another unclassified disease were observed,[179] characterized by a sudden onset of high fever, anorexia and nausea, headache, photophobia, backache and pains in the limbs, occurring chiefly in children and young adults and lasting about a week. The only epidemiologic feature of possible significance was a history of swimming in rivers or lakes by over half of the victims. The authors believe that previous similar outbreaks—an outbreak in Georgia in 1940 also associated with swimming and two outbreaks in California in 1934 and 1935—which may or may not have been of the same disease, were described in 1943 as "pretibial fever." The disease observed did not seem likely to be related to Bullis fever or to Colorado tick

168. Howe, H. A.; Bodian, D., and Wenner, H. A.: Further Observations on the Presence of Poliomyelitis Virus in the Human Oropharynx, Bull. Johns Hopkins Hosp. **76**:19-24 (Jan.) 1945.

169. Horstman, D. M.; Ward, R., and Melnick, J. L.: Persistence of Virus Excretion in the Stools of Poliomyelitis Patients, J. A. M. A. **126**:161-162 (Dec. 23) 1944.

170. Ward, R.; Melnick, J. L., and Horstman, D. M.: Poliomyelitis in Fly-Contaminated Food Collected at an Epidemic, Science **101**:491-493 (May 11) 1945.

171. Kessel, J. F., and Moore, F. J.: Occurrence of Poliomyelitis Virus in Tonsils and Stools of Noncontacts During an Interepidemic Period, Am. J. Hyg. **41**:25-29 (Jan.) 1945.

172. Wyllie, J.: Second Attack of Poliomyelitis After Thirteen Years, Canad. J. Pub. Health **36**:156-159 (April) 1945.

173. Howe, H. A., and Bodian, D.: Poliomyelitis by Accidental Contagion in the Chimpanzee, J. Exper. Med. **80**:383-390 (Nov.) 1944.

174. Melnick, J. L.: Poliomyelitis Virus in the Blood Stream in the Experimental Disease, Proc. Soc. Exper. Biol. & Med. **58**:14-16 (Jan.) 1945.

175. Rasmussen, A. F., Jr.; Waisman, H. A., and Lichstein, H. C.: Influence of Riboflavin in Susceptibility of Mice to Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **57**:92-95 (Oct.) 1944.

176. Kligler, I. J.; Guggenheim, K., and Buechler, E.: Relation of Riboflavin Deficiency to Spontaneous Epidemics of Salmonella in Mice, Proc. Soc. Exper. Biol. & Med. **57**:132-133 (Oct.) 1944.

177. Clark, P. F.; Waisman, H. A.; Lichstein, H. C., and Jones, E. S.: Influence of Thiamine Deficiency in Macaca Mulatta in Susceptibility to Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **58**:42-45 (Jan.) 1945.

178. Schneider, H. A., and Webster, L. T.: Nutrition of the Host and Natural Resistance to Infection, J. Exper. Med. **81**:359-384 (April) 1945.

179. Paul, W. D.; Antes, E. H., and Sahs, A. L.: A Dengue-like Fever Occurring in Iowa During the Poliomyelitis Epidemic of 1943, Arch. Int. Med. **75**: 184-191 (March) 1945.

fever. The authors prefer to call the disease a "dengue-like" fever. Differentiation from poliomyelitis or meningoencephalitis was made by study of the spinal fluid.

Encephalitis.—Encephalitis was found at necropsy in 1 patient with herpes simplex [180] and in 1 with herpes zoster.[181] In both instances, the histologic changes were not specific, and the diagnosis could be made only by association with other factors. In the case of herpes zoster, its etiologic relation with encephalitis was not clear. Mumps meningitis is commented on elsewhere in this review.

In an epidemic of pleurodynia [182] affecting 16 nurses, symptoms of involvement of the central nervous system were striking, suggesting that the causative agent was neurotropic; as many as 76 leukocytes per cubic millimeter were found in the spinal fluid. Five of the attacks were preceded by mild infections of the upper respiratory tract, and gastrointestinal symptoms were common, as in the syndrome viral dysentery already mentioned.

Although mosquitoes were known to be able to convey St. Louis encephalitis to chickens experimentally, new evidence [183] also incriminates chicken mites as interfowl transmitters. Chicken mites and ticks collected in Texas, where epidemics of equine encephalitis occurred, were found to contain the virus of this disease also.[184] They may be the actual natural reservoirs or vectors of both diseases and perhaps of still others. These discoveries suggest certain clear-cut problems in prophylaxis.

Evidence [185] of the existence of even more unknown viruses appears; three neurotropic viruses different from any known ones were isolated from mosquitoes in South America.

Tuberculous Meningitis.—Jennings [186] describes 2 of the few reported cases of recovery from tuberculous meningitis. It seems probable, however, that many more unrecognized nonfatal cases occur which are not diagnosed, either because of the mildness of the symptoms or because the spinal fluid is not studied or tubercle bacilli cannot be found. In other studies, streptomycin had no influence on the course in several cases.

Tetanus.—Under the title of "A New Method of Treating Tetanus," Stern [187] recommends the cisternal injection of antitetanus serum. There is nothing new about this; in fact, the procedure has long been condemned as futile and dangerous. Apparently Soviet investigators have not had access to the papers of Abel and many other clinical reports in the English language.

Rheumatic Fever.—If experiments reported by Copeman [188] can be confirmed, current ideas as to the cause of rheumatic fever must be revised. Blood from a patient with rheumatic fever was injected into 5 volunteers, in 2 of whom mild attacks developed. Blood from these 2 was injected into 4 more volunteers and caused the appearance of symptoms in 1. Transmission was successful once again but failed thereafter. The experiment recalls that of Birkhaug, who caused symptoms to appear in himself by inoculating a filtrate of a strain of nonhemolytic streptococci. Also of interest in this connection is a report by MacNeal and his associates [189] on the production of a nonbacterial form of verrucous endocarditis in rabbits by the intravenous injection of filtered pericardial exudate from a patient with rheumatic carditis. Endocarditis was also caused by the injection of exudates and blood from other patients but with inconstant results. The infection could be propagated from rabbit to rabbit and was apparently grown in embryonated eggs. As usual, difficulties were encountered in differentiating the lesions from those found in rabbits subjected to various other experimental procedures.

In a study of 32 cases, according to Copeman,[190] rheumatic fever was found to be an endogenous disease provoked into clinical significance by preceding conditions which may not be streptococcic in origin, such as exposure, cold

180. Hassin, G. B., and Rabens, I. A.: Herpetic Meningoencephalitis: Clinical-Pathologic Report of Case, J. Neuropath. & Exper. Neurol. **3**:355-367 (Oct.) 1944.

181. Krumholz, S., and Luhan, J. A.: Encephalitis Associated with Herpes Zoster: Report of Case, Arch. Neurol. & Psychiat. **53**:59-67 (Jan.) 1945.

182. McConnell, J.: An Epidemic of Pleurodynia with Prominent Neurologic Symptoms and No Demonstrable Cause, Am. J. M. Sc. **209**:41-48 (Jan.) 1945.

183. Smith, M. G.; Blattner, R. J., and Heys, F. M.: The Isolation of the St. Louis Encephalitis from Chicken Mites (Dermanyssus Gallinae in Nature), Science **100**:362-363 (Oct. 20) 1944.

184. Sulkin, S. E.: Recovery of Equine Encephalomyelitis Virus (Western Type) from Chicken Mites, Science **101**:381-383 (April 13) 1945.

185. Roca-Garcia, M.: The Isolation of Three Neurotropic Viruses from Forest Mosquitoes in Eastern Colombia, J. Infect. Dis. **75**:160-169 (Sept.-Oct.) 1944.

186. Jennings, G. H.: Recovery from Tuberculous Meningitis, Lancet **1**:466-467 (April 14) 1945.

187. Stern, L. A.: A New Method of Treating Tetanus, Am. Rev. Soviet Med. **1**:540-543 (Aug.) 1944.

188. Copeman, W. S. C.: Experimental Transmission of Rheumatic Fever, Ann. Rheumat. Dis. **4**:37-39 (Dec.) 1944.

189. MacNeal, W. J.; Blevins, A.; Slavkin, A. E., and Scanlon, H.: Experimental Verrucous Endocarditis, Science **101**:415-416 (April 20) 1945.

190. Copeman, W. S. C.: Observations on the Natural History of Acute Rheumatic Fever, Ann. Rheumat. Dis. **4**:11-17 (Sept.) 1944.

and fatigue. In only a few instances was there a suggestion of transmission by droplets or by air. He believes rheumatic fever to be basically an acute progressive febrile fibrositic reaction localized in tendon sheaths near joints.

A symposium on rheumatic fever is reported in the October 21 issue of the *Journal of the American Medical Association*. In it Wilson and Lubschez express doubt that the role of hemolytic streptococcic infection in precipitating rheumatic occurrences has been proved by several studies in which sulfonamide prophylaxis supposedly reduced the incidence of the disease. The published data, they state, do not meet the basic requirements for adequate biostatistical analysis. On the other hand, according to Jones, epidemiologic data from military sources seem to indicate close association of rheumatic disease with hemolytic streptococcic infections. He outlines the criteria for reasonably certain diagnosis of the disease. He, like Wilson, also refuses to accept as proved the evidence that sulfonamide prophylaxis is reliable in preventing recurrences of the disease and properly regards it still as an experimental measure. Thomas maintains her previous view that sulfonamide prophylaxis is the most effective measure of preventing recurrences. She recommends 1 Gm. of sulfadiazine daily for at least five years. One of her patients has received this dose for eight years. One wonders if the evidence of superiority of penicillin for hemolytic streptococcic infections will cause a change of these views.

Not long ago Coburn recommended massive doses of sodium salicylate to be given intravenously for the treatment of rheumatic fever. Subsequently, deaths and severe complications were reported [191] in patients receiving large doses. Salicylic poisoning was seldom considered in the past, but it is, nevertheless, dangerous.

Rheumatoid Arthritis.—Freund and his associates [192] report a novel view of the pathology of rheumatoid arthritis. In 14 patients they found inflammatory nodules widely disseminated in the peripheral nerve trunks and muscles. Control studies on nonarthritic patients failed to show these lesions. The changes, they believe, serve to explain the clinical manifestations of the disease and show that it is a systemic one not confined to the joints. One wonders why such striking changes had not been noted or reported by other investigators before, whether in certain cases they may not be an effect rather than a cause and what their relation is to the well known subcutaneous nodules found in this disease.

191. Ashworth, C. T., and McKernie, J. F.: Hemorrhagic Complications with Death Probably from Salicylate Therapy, J. A. M. A. **126**:806-810 (Nov. 25) 1944.

192. Freund, H. A.; Steiner, G.; Leichtentritt, B., and Price, A. E.: Nodular Polymyositis in Rheumatoid Arthritis, Science **101**:202-203 (Feb. 23) 1945.

OTHER VIRAL DISEASES

Mumps.—With the idea in mind of immunizing children against mumps at an age when the disease is supposedly not dangerous, an epidemic was permitted to spread unchecked in a school.[193] Out of 161 exposed children, 114 were susceptible. Of these, 62 contracted mumps, 4 with encephalitis, 1 with orchitis and 1 with pancreatitis. Besides these, 10 members of the families of these children had mumps. The school physician decided it would be unwise to repeat the experiment. Experimental evidence [194] suggests that in most circumstances mumps, in contrast with chickenpox, is not a true air-borne disease.

In experiments by Enders and his associates,[195] monkeys were infected by the intraparotid injection of saliva from patients. An antigen appeared in the gland which reacts with the serum of convalescent monkeys. In human beings, a specific antibody appears in the serum regularly during and after the disease. Specific dermal hypersensitivity and complement-fixing antibodies in the serum developed in convalescent patients. The complement fixation test is especially valuable in the difficult diagnosis of mumps encephalitis when parotitis is minimal, delayed or absent. The reaction was positive in 16 of 50 patients with encephalitis without involvement of the parotid gland. It would probably be valuable also in the diagnosis of mumps pancreatitis or orchitis.

Mumps virus in large amounts for use in the complement fixation test can be obtained from chick embryo cultures.[196] Egg virus facilitates the possible development of vaccine, material for cutaneous tests and other aids in the study of mumps.

193. Levine, M. I.: Sponsored Epidemic of Mumps in a Private School, Am. J. Pub. Health **34**:1274-1276 (Dec.) 1944.

194. Habel, K.: Mumps and Chickenpox as Air-Borne Diseases, Am. J. M. Sc. **209**:75-78 (Jan.) 1945.

195. Enders, J. F.; Kane, L. W.; Cohen, S., and Levens, J. H.: Immunity in Mumps: I. Experiments with Monkeys (Macacus Mulatta), J. Exper. Med. **81**:93-118 (Jan.) 1945. Enders, J. F.; Cohen, S., and Kane, L. W.: II. Development of Complement-Fixing Antibody and Dermal Hypersensitivity in Human Beings Following Mumps, ibid. **81**:119-136 (Jan.) 1945. Kane, L. W., and Enders, J. F.: III. Complement Fixation Test as Aid in Diagnosis of Mumps Meningoencephalitis, ibid. **81**:137-150 (Jan.) 1945.

196. Habel, K.: Cultivation of Mumps Virus in the Developing Chick Embryo and Its Application to Studies of Immunity to Mumps in Man, Pub. Health Rep. **60**:201-217 (Feb. 23) 1945.

That mumps should be considered a general systemic infection is pointed out by Swedish clinicians.[197] The parotid glands are usually involved but not always. Among 458 patients in an epidemic, changes in the spinal fluid indicated meningeal involvement in 65 per cent. In 10 per cent, meningeal involvement preceded swelling of the parotid gland. In support of the view of Enders just mentioned, mumps is suggested as a cause of certain undiagnosed attacks of lymphocytic meningitis. From electrocardiographic evidence Rosenberg [198] concludes that, contrary to general belief, the myocardium is often involved during mumps. Of 104 patients, transient electrocardiographic changes appeared in 16.

Measles.—Gamma globulin is better than placental globulin for the prophylaxis of measles.[199] Among 814 children exposed to the disease and treated, none had regular measles; 78 per cent were completely protected, and the rest had mild attacks. Concentrated gamma globulin, when given in the first six days after exposure to the disease, will protect 3 out of every 4 persons if it is given in doses of 0.08 to 0.1 cc. per pound (0.5 Kg.) of body weight.[200]

Smallpox.—Stevenson [201] points out that vaccination against smallpox usually gives reliable protection but in numerous instances it fails. There is no justification for the opinion that vaccination within a few days after exposure to smallpox will invariably give immunity to it. Unexplained variations in immunity response to vaccine occur in different persons. Variations of potency or in the immunizing power of the vaccine cannot always be blamed for failures.

In an outbreak among a supposedly highly immunized group,[202] 96 per cent had been vaccinated at some time, 70 per cent within two years and 16 per cent within two months. Great variations also occur in the clinical manifestations of the disease itself. Accurate clinical diagnosis in the early stages is often impossible, and little reliance should be placed on details of the typical textbook descriptions, including the three to four day fever, backache and the supposed characteristic eruption. The eruption may mimic those of measles or chickenpox. Diagnosis was greatly aided by a new test [203] consisting of making scrapings of a papule, staining them on a specially prepared slide and examining them for elementary bodies. These bodies are much more numerous than those in the lesions of chickenpox. The results of the test were positive in 77 out of 80 cases. It is rapid and easily eliminates probable diagnoses of chickenpox, measles or typhus. The Paul rabbit eye test is less reliable and takes three days to do.

Psittacosis.—Evidence is presented [204] that epizootics among pigeons may be caused by two viruses simultaneously, one a psittacosis-like virus (ornithosis) and the other a new one called INI (intranuclear inclusion) virus. The latter is pathogenic for pigeons but not for rabbits, guinea pigs or mice.

Of 113 mixed Amazon parrots and parakeets impounded by quarantine regulations in Brownsville, Texas, 108 died (97 per cent) from psittacosis and bacterial infections, especially those with the Salmonella group of bacilli.[205]

Yellow Fever.—For the first time [206] yellow fever was discovered in a wild animal in its natural habitat in South America. A sick monkey was trapped and died from the disease. The discovery favors the view that the reservoir of jungle yellow fever is in animals, from which it is spread to human beings. Antibodies, but no virus, were found in the blood of the other monkeys and in opossums, suggesting past infections with yellow fever virus.

Other Studies on Viruses.—Distemper virus, like the other filtrable viruses, may be modified by passage in hosts other than the usual ones.[207] By passing through ferrets, the virulence of canine distemper virus for foxes or dogs declined, and

197. Bang, H. O., and Bang, J.: Involvement of the Central Nervous System in Mumps, Acta med. Scandinav. **113**:487-505 (April) 1943.

198. Rosenberg, D. H.: Electrocardiographic Changes in Epidemic Parotitis (Mumps), Proc. Soc. Exper. Biol. & Med. **58**:9-11 (Jan.) 1945.

199. Greenberg, M.; Frant, S., and Rutstein, D. D.: "Gamma Globulin" and "Placental Globulin," J. A. M. A. **126**:944-947 (Dec. 9) 1945.

200. Janeway, C. A.: The Use of Concentrated Human Serum γ-Globulin in Prevention and Attenuation of Measles, Bull. New York Acad. Med. **21**:202-222 (April) 1945.

201. Stevenson, W. D. H.: Vaccination Against Smallpox: Apparent Anomalies in Protection, Lancet **2**:697-700 (Nov. 25) 1944.

202. Illingworth, R. S., and Oliver, W. A.: Smallpox in the Middle East: Lessons from One Hundred Cases, Lancet **2**:681-685 (Nov. 25) 1944.

203. van Rooyen, C. E., and Illingworth, R. S.: Laboratory Test for Diagnosis of Smallpox, Brit. M. J. **2**:526-529 (Oct. 21) 1944.

204. Smadel, J. E.; Jackson, E. B., and Harman, J. W.: A New Virus Disease of Pigeons: I. Recovery of the Virus, J. Exper. Med. **81**:385-397 (April) 1945.

205. Dunnahoo, G. L., and Hampton, B. C.: Psittacosis: Occurrence in the United States and Report of 97 per cent Mortality in a Shipment of Psittacine Birds While Under Quarantine, Pub. Health Rep. **60**:354-357 (March 30) 1945.

206. Fosdick, R. B.: The Rockefeller Foundation: A Review for 1944, p. 36.

207. Green, R. G.: Zoologic and Histologic Modification of the Distemper Virus by Ferret Passage, Am. J. Hyg. **41**:7-24 (Jan.) 1945.

after fifty passages the virus caused only symptomless infection; after further passage, no infection resulted.

Habel [208] obtained better results in the protection of animals against rabies by using a concentrated rabies-immune rabbit serum with the usual vaccine method of prophylaxis. Serum prophylaxis combined with vaccine prophylaxis gave even better results. Trial in human beings is warranted.

According to Kramer and his co-workers,[209] who tested the therapeutic and prophylactic action of a wide variety of chemical compounds on neurotropic virus infections in mice, none of the agents had any value. Some effect of sulfonamide compounds and penicillin has been reported on infections of the psittacosis group, but there is still a question as to whether the causative agents are true filtrable viruses.

With an ingenious technic,[210] electron micrography can now show three dimensional views of virus particles to give new information about their size and shape. In Beard's studies,[211] electron micrography showed unmistakable evidence of differentiation within virus particles, causing him to favor the idea that viruses are not mere aggregates of molecules but resemble relatively more highly organized bacteria in their shape and internal makeup.

Tularemia.—In a study [212] in which Bacterium tularense was found to be extremely polymorphous, Foshay and Hesselbrock found some forms to be so minute as to resemble certain elementary bodies. In filtration tests with gradocol membranes, these minute pathogenic forms passed through and developed into larger units after their inoculation in animals.

A long list of naturally infected vertebrates was published.[213]

In a clinical report [214] on studies made without proper controls, 61 patients with tularemia are said to have been promptly cured by the intravenous injection of a solution of bismuth sodium tartrate. The details of the investigation are so meager as to render further judgment of the report impossible. In experimental studies [215] on guinea pigs, a variety of medicaments, including sulfonamide compounds, penicillin, iodide and bismuth compounds, an arsenical, an antimony compound and antitularemic serum, were found to be of no value in treatment. It is possible that streptomycin will prove to be the most effective therapeutic agent.

Many more persons are bitten by rats than is usually thought.[216] In a study of an area of 2 square miles (approximately 5 square kilometers) in Baltimore, it was learned that a minimum of 93 persons were bitten in a four year period and in 7 (14 per cent) rat bite fever developed.

Rickettsial Diseases.—Attention is called to the dangers of circulatory collapse associated with typhus [217] and with Rocky Mountain spotted fever [218] and to the need for appropriate supportive therapy. A great deal of nonsense has also been advocated. In one instance,[219] sulfonamide compounds were given "as a matter of routine" before diagnosis was made; then penicillin was given, and the fever fell. In another,[218] quinine sulfate was given, despite the current shortage, then, among other things, metaphen intravenously for ten days, then calcium chloride and vitamins intravenously, then sulfadiazine and finally roentgenotherapy. The patient recovered anyway.

A report [220] on the use of antityphus serum is not impressive. Serum apparently had a bene-

208. Habel, K.: Seroprophylaxis in Experimental Rabies, Pub. Health Rep. **60**:545-560 (May 18) 1945.

209. Kramer, S. D.; Geer, H. A., and Szobel, D. A.: The Chemoprophylactic and Therapeutic Action of a Wide Variety of Chemical Compounds on True Neurotropic Virus Infections in Mice, J. Immunol. **49**:273-314 (Nov.) 1944.

210. Williams, R. C., and Wyckoff, R. W. G.: Electron Shadow-Micrography of Virus Particles, Proc. Soc. Exper. Biol. & Med. **58**:265-270 (March) 1945.

211. Beard, J. W.: The Ultracentrifugal, Chemical and Electron Micrographic Characters of Purified Animal Viruses, Proc. Inst. Med. Chicago **15**:294, 1945.

212. Foshay, L., and Hesselbrock, W.: Some Observations on the Filtrability of Bacterium Tularense, J. Bact. **49**:233-236 (March) 1945.

213. Burroughs, A. L.; Holdenried, R.; Longanecker, D. S., and Meyer, K. F.: A Field Study of Latent Tularemia in Rodents with a List of All Known Naturally Infected Vertebrates, J. Infect. Dis. **76**:115-119 (March-April) 1945.

214. Jackson, W. W.: The Treatment of Tularemia with Intravenous Bismuth Sodium Tartrate, Am. J. M. Sc. **209**:513-520 (April) 1945.

215. Bell, J. F., and Kalm, O. B.: Efficacy of Some Drugs and Biologic Preparations as Therapeutic Agents for Tularemia, Arch. Int. Med. **75**:155-158 (March) 1945.

216. Richter, C. P.: Incidence of Rat Bites and Rat Bite Fever in Baltimore, J. A. M. A. **128**:324-326 (June 2) 1945.

217. Woodward, T. E., and Bland, E. F.: Clinical Observations in Typhus Fever with Special Reference to the Cardiovascular System, J. A. M. A. **126**:287-290 (Sept. 30) 1944.

218. Harrell, G. T.; Venning, W., and Wolff, W. A.: The Treatment of Rocky Mountain Spotted Fever, J. A. M. A. **126**:929-934 (Dec. 9) 1944.

219. Edmunds, P. K.: Rocky Mountain Spotted Fever: Treatment with Penicillin, Rocky Mountain M. J. **41**:910-912 (Dec.) 1944.

220. Stevens, R. S.: Louse-Borne Typhus Fever: Trial of Serum Treatment, Lancet **1**:106-109 (Jan. 27) 1945.

ficial effect in modifying the severity of the disease in a few patients.

EXOTIC DISEASES

Sapero and Butler [221] review the infectious diseases which caused our naval forces the most concern in the South Pacific area: namely, malaria, bacillary dysentery, dengue, filariasis, infectious hepatitis and tsutsugamushi fever (scrub typhus). They point out how effectively malaria can be controlled even under combat conditions, chiefly by the control and elimination of the breeding areas of anopheles mosquitoes, by the proper use of chemical repellents and insecticides, by screening and by medication. One of the greatest factors in the prevention of malaria, dengue and filariasis was the separation or isolation of our personnel from infected natives who served as sources of infection. Dengue is also preventable by effective measures to prevent the breeding of mosquitoes and their access to patients with the disease. Bacillary dysentery was effectively controlled by reducing the number of flies by proper disposal of garbage and fecal matter and by the use of screens.

Malaria.—In a study [222] of soldiers returning to this country with malaria contracted in the South Pacific area, the acute recurrent attacks, mostly of Plasmodium vivax origin, were found to be relatively mild. Quinacrine hydrochloride was effective in ridding the blood of parasites and in controlling symptoms. The rate of recurrences diminished with the passage of time. In spite of the good immediate results of therapy with quinacrine hydrochloride, the large number of relapses is a problem. Many patients also complain of not feeling well between attacks. Symptoms suspected as psychoneurotic in origin were often encountered.

The apparent transmission of malaria from a soldier returned from the Pacific area to 2 persons is reported [223] from an area in Oregon previously free from the disease. Mosquitoes were abundant at the time (Anopheles punctipennis and maculipennis).

Sulfadiazine is of no value in preventing relapses of malaria caused by a strain of P. vivax malaria in the Southwest Pacific area.[224] The drug should not be used. The rate of relapse of this form of malaria is high and is not controlled by quinine, quinacrine hydrochloride (atabrine) or pamaquine naphthoate (plasmochin). It is also not generally known that there are striking clinical differences among infections caused by different strains of the same type and between naturally acquired and induced malaria; induced malaria is easily controlled with quinine, and there are no relapses.

Plasmodium malariae is inactivated by exposure to roentgen rays and is most sensitive during the process of division.[225]

Report [226] is made of the first successful cultivation of P. knowlesi in culture medium.

Dengue.—By passage of the virus of dengue through mice it becomes modified to such an extent that it may serve as an effective vaccine.[227]

Filariasis.—Extensive studies are being made on filariasis. In the Pacific area, military personnel have shown evidence of infections clinically [228] and histologically [229] three months after arrival. The usual history is of painful intermittent swelling of the testicle for weeks or months. Diagnosis is made by biopsy, by the finding of microfilarias in the blood and by observation of calcified worms by roentgenography. Derivatives of antimony, including lithium antimony thiomalate, are giving encouraging results in treatment.[230]

221. Sapero, J. J., and Butler, F. A.: Highlights on Epidemic Diseases Occurring in Military Forces in the Early Phases of the War in the South Pacific, J. A. M. A. **127**:502-506 (March 3) 1945.

222. Gordon, H. H., and others: Clinical Features of Relapsing Plasmodium Vivax Malaria in Soldiers Evacuated from the South Pacific Area, Arch. Int. Med. **75**:159-167 (March) 1945.

223. Osgood, S. B.: Malaria and the Returning Soldier, J. A. M. A. **128**:512-513 (June 16) 1945.

224. Coggeshall, L. T.; Martin, W. B., and Bates, R. D.: Sulfadiazine in Treatment of Relapsing Malarial Infections Due to Plasmodium Vivax, J. A. M. A. **128**:7-8 (May 5) 1945.

225. Bennison, B. E., and Coatney, G. R.: Inactivation of Malarial Parasites by X-Rays, Pub. Health Rep. **60**:127-129 (Feb. 2) 1945.

226. Ball, E. G., and others: In Vitro Growth and Multiplication of the Malaria Parasite, Plasmodium Knowlesi, Science **101**:542-544 (May 25) 1945.

227. Sabin, A. B., and Schlesinger, R. W.: Production of Immunity to Dengue with Virus Modified by Propagation in Mice, Science **101**:640-642 (Jan. 22) 1945.

228. King, B. G.: Early Filariasis: Diagnosis and Clinical Findings, Am. J. Trop. Med. **24**:285-298 (Sept.) 1944. Byrd, E. E.; St. Arnant, L. S., and Bromberg, L.: Studies on Filariasis in the Samoan Area, U. S. Nav. M. Bull. **44**:1-20 (Jan.) 1945.

229. Wartman, W. B.: Lesions of Lymphatic System in Early Filariasis, Am. J. Trop. Med. **24**:281-284 (Sept.) 1944; Clinicopathologic Study of Early Filariasis with Lymph Node Biopsies, U. S. Nav. M. Bull. **44**:27-36 (Jan.) 1945.

230. Research on Filariasis, Foreign Letters, J. A. M. A. **127**:475 (Feb. 24) 1945.

Among 5,000 persons examined [231] for filariasis in Belém, Brazil, 11 per cent harbored microfilarias (Wuchereria bancrofti). The principal vector is the mosquito Culex fatigans, 12 per cent of which were found on examination to carry the parasite.

A case of American leishmaniasis caused by Leishmania braziliensis apparently originating in the United States was reported.[232] The disease is probably much more common in this country than is realized though probably unrecognized.

Schistosomiasis.—Although, as reported by Koppisch several years ago, no snails in this country are known to serve as natural hosts to the causative agent of schistosomiasis, Schistosoma mansoni, evidence now shows [233] that potential carriers do exist. A native snail, Tropicorbis havanensis, was experimentally infected with S. mansoni. The acquisition of a natural infection is theoretically possible if these snails become exposed to the excreta of returned military personnel suffering from the disease.

An important point is raised by Bercovitz and his associates,[234] who show that in schistosomiasis, as in other diseases, so-called carriers may actually have the disease and that the actual incidence of the disease, including all mild forms, is much greater than is usually believed. By proctoscopic examination actual ulcerations were found in 60 per cent of 155 otherwise healthy Puerto Ricans who shed ova of S. mansoni in their feces. According to the authors, healthy carriers of the disease are to be regarded as infected persons.

Granuloma Inguinale.—The causative agent of granuloma inguinale has been cultivated in chick embryos.[235] A new name, Donovania granulomatis, is proposed for the micro-organism, which is probably a bacterium. Washed suspensions of the agent when injected intradermally elicit a strong reaction in twenty-four hours in the active stage of the disease. A mucoid substance, probably capsular in origin, when mixed with serum caused precipitation and complement fixation. These reactions may be of diagnostic value.

Pinta.—After previous reported attempts had failed, two Cubans [236] successfully transmitted pinta to rabbits by inoculating them with Treponema carateum obtained from a patient. A papule developed one hundred and five days later at the point of inoculation in 1 of 4 rabbits. A volunteer contracted the disease when inoculated with material from the rabbit.

Leprosy.—By using a special stain, non-acid-fast, "zoogleal" forms or phases of both Mycobacterium tuberculosis and Myocobacterium leprae can be shown.[237] The existence of the organisms in such forms may account for the difficulty in finding them in certain instances unless the special staining technic is used.

A new disease in horses and man, stachybotryotoxicosis, is described by Drobotko.[238] In horses there are necrotic ulcers in the mouth and throat, hemorrhage, lymphadenopathy and leukopenia reminiscent of glanders, yet the disease does not seem to be contagious and is apparently contracted by the consumption of hay containing the mold Stachybotrys alternans. The fact that healthy horses fed moldy hay and feed mixed with cultures of the mold always become infected suggests the etiologic relation. Persons are occasionally infected by contact with the infected hay and have erythema, pharyngitis and rhinitis with bloody exudate, cough and leukopenia without fever. The author goes far afield when he suggests that this mold may be the cause of acute agranulocytosis.

ANTIBODY FORMATION

After lying dormant for several years,[239] the subject of the site of formation of antibodies has been revived, with special emphasis on the role

231. Causey, O. R.; Deane, M. P.; DaCosta, O., and Deane, L. M.: Studies on the Incidence and Transmission of Filaria, Wucheria Bancrofti, in Belém, Brazil, Am. J. Hyg. **41**:143-149 (March) 1945.

232. Stewart, C. D., and Pilcher, J. F.: American Leishmaniasis: Report of an Autochthonous Case, Arch. Dermat. & Syph. **51**:124-128 (Feb.) 1945.

233. Cram, E. R.; Jones, M. F., and Wright, W.: A Potential Intermediate Host of Schistosoma Mansoni, Science **101**:302 (March 23) 1945.

234. Bercovitz, Z. T.; Rodriguez-Molina, R.; Hargrave, D. W.; Dickie, J. D., and Green, C. E.: Studies on Human Schistosoma Mansoni Infections: I. Proctoscopic Picture in Asymptomatic Schistosomiasis Mansoni Infections, J. A. M. A. **125**:961-963 (Aug. 5) 1944.

235. Anderson, K.; DeMonbreun, W. A.. and Goodpasture, E. W.: An Etiologic Consideration of Donovania Granulomatosis Cultured from Granuloma Inguinale (Three Cases) in Embryonic Yolk, J. Exper. Med. **81**:25-39 (Jan.) 1945. Anderson, K.; Goodpasture, E. W., and DeMonbreun, W. A.: Immunologic Relationship of Donovani Granulomatosis to Granuloma Inguinale, ibid. **81**:41-50 (Jan.) 1945.

236. León-Blanco, F., and Oteiza, A.: The Experimental Transmission of Pinta, Mal del Pinto or Curate to the Rabbit, Science **101**:309-311 (March 23) 1945.

237. Alexander-Jackson, E.: Non-Acid-Fast Forms of the Mycobacterium of Human Leprosy, Science **101**:563-564 (June 1) 1945.

238. Drobotko, V. G.: Stachybotryotoxicosis: A New Disease of Horses and Humans, Am. Rev. Soviet Med. **2**:238-242 (Feb.) 1945.

239. Reimann, H. A.; Medes, G., and Fisher, L.: The Origin of Blood Proteins, Folia haemat. **52**:187-202, 1934.

of lymphocytes. In one study,[240] lymphocytes were said to contain a protein probably identical with gamma globulin and were thought to be the site of origin of immune globulin, but the authors make no reference to previous studies on this point or to any others along similar lines. In another recent report,[241] a somewhat broader and perhaps better view is given—namely, that lymphocytes either produce or adsorb antibodies, and other circulating and fixed leukocytic cells also participate in antibody formation. According to another view,[242] lymphocytes do not adsorb antibodies but probably are the site of a change of gamma globulin into an immune substance. Most of these views were held for many years and were embodied in a monograph[243] published in 1941.

Other experiments[244] indicate a control of the number of lymphocytes in the blood and perhaps in other places in the body by secretions of the adrenal cortex. If lymphocytic tissue is as intimately connected with immune responses of the body as is believed by the authors cited in the preceding paragraph, these observations will focus much attention on the role of the anterior pituitary and adrenal glands in the hormonal control of immunity, especially of immunity to infectious diseases accompanied with either lymphopenia or lymphocytosis.

240. Dougherty, T. F.; Chase, J. H., and White, A.: The Demonstration of Antibodies in Lymphocytes, Proc. Soc. Exper. Biol. & Med. **57**:295-298 (Nov.) 1944.

241. Ehrich, W. E., and Harris, T. N.: The Site of Antibody Formation, Science **101**:28-31 (Jan. 12) 1945. Harris, T. N., and Ehrich, W. E.: The Role of the Lymphocyte in Antibody Formation, J. Exper. Med. **81**:73-83 (Jan.) 1945.

242. Kass, E. H.: The Occurrence of Normal Serum Gamma-Globulin in Human Lymphocytes, Science **101**: 337-338 (March 30) 1945.

243. Burnett, F. F.; Freeman, M.; Jackson, A. V., and Bush, D.: The Production of Antibodies, Melbourne, Australia, Macmillan & Co., Ltd., 1941.

244. Reinhardt, W. O., and Li, C. H.: Depression of Lymphocyte Contact of Thoracic Lymph by Adrenocorticotrophic Hormone, Science **101**:360-361 (April 6) 1940.

According to Cannon[245] there is little hope that optimal nutrition will activate bacteriostatic agents in the defense against infection but inanition may induce a decrease of resistance by interfering with the synthesis of serum globulins, which are important in antibody formation. Globulins seem to play a role in the nonspecific defense aganist infection.[246] Evidence points more and more to the view that certain aspects of resistance to infection are nutritional or hormonal, but many factors are still unknown.

In dietary studies[247] like those commented on in the paragraphs on poliomyelitis, rats fed a diet deficient in certain vitamins, except thiamine, were more resistant to pneumococcic infections than well fed rats. Inanition itself had no apparent effect on their resistance. Genetic factors must also be considered in interpreting the results of experimental studies.[178]

245. Cannon, P. R.: Proteins in Resistance to Infection, J. A. M. A. **128**:360-362 (June 2) 1945.

246. Reimann, H. A.: The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection, Ann. Int. Med. **6**:362-374 (Sept.) 1932.

247. Robinson, H. J., and Siegel, H.: The Influence of B Vitamin on the Resistance of Rats to Induced Pneumococcal Lobar Pneumonia, J. Infect. Dis. **75**: 127-133 (Sept.-Oct.) 1944.

CORRECTION

In the article by Major Robert M. Finks and Captain Richard W. Blumberg entitled "Epidemic Hepatitis With and Without Jaundice: Some Clinical Studies on Two Hundred and Fifty-Five Patients Among Troops in a Combat Zone" in the August issue (ARCH. INT. MED. **76**:102, 1945), sixteen lines from the bottom of the first column on page 110 1.74 mg. of bilirubin should read 174 mg. In the second column of the same page, fifth line of the second paragraph under "Pathologic Data," the word "red" should be "green."

In their proof, which was returned after publication of the article, the authors added the following statement to the fourth new paragraph in the second column on page 111:

"The various tests of hepatic function, such as hippuric acid synthesis and sulfobromophthalein excretion, although used in only a few cases, seemed to be of definite value in diagnosis of this syndrome."